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A Record of the Progress of Pharmacy and the Allied Sciences

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Vol. 102 SEPTEMBER, 1930 No. 9

CONTENTS

Editorial:
Now That the Election Is Over 393

Selected Editorial:
The Neglect of Pharmacology. Reprinted From the *Journal of the American Medical Association* 395

Original Articles:
Solution of Magnesium Citrate. By Edward W. Rees, Philadelphia, Pa. 398

A Critical Study of Methods of Assay of Cinchona Hydrate. By [illegible] Watson, Winnipeg, Manitoba 399

The Daturas. By F. B. Kilmer, New Brunswick, N. J. 407

The Mercuration of Phthaleins in Neutral Solution With Bichloride of Mercury. By Frederick R. Greenbaum, Chicago, Ill. 409

Phytochemical Notes.—From the Laboratory of Edward Kremers No. 102. A Preliminary Study of Digitalis Seed. By S. H. Culver, Madison, Wis. 412

Medical and Pharmaceutical Notes 417

News Items and Personal Notes 421

Book Reviews 429

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THE AMERICAN
JOURNAL OF PHARMACY

VOL. 102 SEPTEMBER, 1930 NO. 9

EDITORIAL

NOW THAT THE ELECTION IS OVER

USUALLY the American Pharmaceutical Association, in the conduct of its ramified offices, carries on with an air of genuine dignity and decorum. This has gained for the Association, throughout its existence, a deserved reputation for stability and seriousness of purpose.

Once in a great while, however, and that is once too often, the august body breaks out in a rash—not indeed as a reflection of internal disorder—but rather through the external ministry of an ill-advised procedure.

Such was the case recently with the national election—when President-elect Adams of Texas earned the much deserved honor.

By using pre-election methods that savored of high school election hokum certain (or uncertain) well-meaning friends and neighbors of the President-elect stole from him much of the genuine satisfaction which would have come to him in the natural order of things and without these undignified efforts of his well wishers.

President-elect Adams deserves this national honor from his fellow-pharmacists, and we dare say he has been embarrassed by the exuberance and exaggerations of his friends.

Pre-election propaganda should be unheard of in the American Pharmaceutical Association. Merit alone should make the choice.

IVOR GRIFFITH.

SELECTED EDITORIAL

THE NEGLECT OF PHARMACOLOGY*

A SURVEY of American medical schools is likely to give one a distinct impression that pharmacology has been somewhat neglected as a medical discipline in this country. In some of the universities it is relegated to a "joint department," usually in company with biochemistry, just as the latter was submerged under the label of physiology for many years and so remains in some of the European centers. In an informative and stimulating presidential address, delivered at the pharmacopœial convention in Washington a few weeks ago, Reid Hunt [1] of Harvard University Medical School referred to the opportunities that lie before the pharmacologic investigator of today and deplored the lack of adequate support that his science has received in the United States. To those who are wont to assume that empiricism has been responsible for most of the drugs with specific action now in use and who recall that mercury, quinine, opium alkaloids and other potent therapeutic agents antedate modern scientific ventures comes the reminder that pharmacology has made malaria, amebic dysentery, syphilis, yaws and other diseases yield to synthetic drugs of the last half century. Hunt reminds us that among the important therapeutic agents added in this period to the pharmacopœia are the arsphenamines, every effective hypnotic, analgesics such as acetanilid, the salicylates, the nitrites, bromides, the antitoxins, and nearly all antiseptics. He adds the unpleasant reminder that the United States has made scarcely a single original contribution to this list. Hunt is responsible for the allegation that "at the present time, there is scarcely a university pharmacological laboratory in the United States the equal of a number in Germany forty or even fifty years

*Reprinted from the *Journal of the American Medical Association.*

[1] Hunt, Reid: Promotion of Medicine and Pharmacy, *Science* 72:49 (July 18) 1930.

ago." Part of the indifference to pharmacology is perhaps attributable to the comparative "therapeutic nihilism" of the present generation of physicians. They bank largely on the *vis medicatrix naturae,* the healing power of nature that is a saving grace for many cults. Nature, Hunt remarks, is certainly not very active in healing cancer, syphilis, tetanus, amebic dysentery, yaws, diabetes, myxedema, hookworm and other diseases, many of which may now be relieved or cured by drugs. He cites the famous remark of Benjamin Rush that nature should be turned outdoors and efficient art substituted for her. Thousands of new organic compounds have been prepared in recent years; hundreds of them deserve pharmacologic investigation. Surely here is an immediate challenge demanding the earnest support of all who are interested in medical progress. It calls for more than half-hearted tolerance and indifferent attitudes. Promising opportunities beckon to the talented investigator endowed with perseverance and patience.

ORIGINAL ARTICLES

SOLUTION OF MAGNESIUM CITRATE

By Edward W. Rees, B. Sc.

IN ORDER to study the effects of long standing and other points of interest bearing upon Solution of Magnesium Citrate U. S. P. X, sixty-nine samples were obtained which varied in age from one to three years. These solutions were made strictly by the U. S. P. X process in a relatively small (500-bottle lot) manufacturing laboratory and consisted of the lot samples from many different manufacturing operations. These samples were bottled in the usual "patent-stoppered" bottles with rubber washers. They had held their flavor very satisfactorily and while the amount of CO_2 present was not determined, all of the samples were well charged with CO_2 gas, giving evidence that very little had been lost by leakage. The liquid portion of the majority of the samples was quite normal, but in a few cases the color had changed to dark brown. The cause of this was not determined although it was probably due to caramelization. In a great many bottles a white sediment was present, varying in weight up to 8.5 grams. These deposits were crystalline in appearance, with some of the crystals very large and others small. Of the sixty-nine samples available, forty-four contained a deposit, or 64 per cent.

The first step undertaken was to determine chemically how the solutions conformed to the U. S. P. X requirements. The methods used were strictly those detailed in the U. S. P. X. The free acidity, the total acidity and the magnesium oxide content were first determined. The tests for tartaric acid and sulphate were also applied and none of the samples was found to contain either of these impurities. Of the sixty-nine samples, twenty-six were examined by the above-named methods. The results will be found in table one, with identification numbers, dates of manufacture, condition of samples, free acidity, total alkalinity, and magnesium oxide content.

Following these analyses it was decided to check up solutions of magnesium citrate bought on the market. Accordingly sixteen samples were purchased at various drug stores in Philadelphia and subjected to the same analyses as the other samples. The results will be found in table two. These commercial samples were not more than two weeks old and were strongly charged with CO_2 when opened for

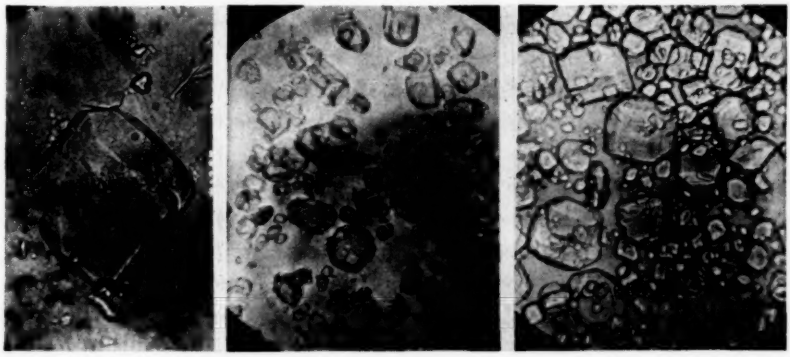
analysis. Some were closed with "patent stoppers," others with "crown stoppers." The analyses of these two sets of samples revealed interesting facts.

In the samples that were from one to three years old, the free acidity remained in excess of the U. S. P. X requirements. (Bottles numbered up to 5881.) The total acidity was low in all but seven samples one of which was made by the author according to the U. S. P. X formula; sixteen contained crystal deposit and this probably accounted for their being low in magnesium content and total acidity. Out of the ten which contained no crystals or deposits of any kind, only five came near being normal in every respect.

The crystal deposit present in the bottles was analyzed for its magnesium oxide content, moisture and citric acid content. The theoretical content of normal tribasic magnesium citrate is 10.37 per cent. for magnesium (magnesium oxide 17.20), moisture 35.86 per cent. and citric acid 59.74 per cent. The crystals analyzed were found to be close to these thetoretical figures with the magnesium ranging from 10.35 per cent. (magnesium oxide 17.1) to 10.55 per cent. (magnesium oxide 17.4).

The carbon content was determined by the combustion method (oxidation of carbon to carbon dioxide) and found to be 20.05 per cent., checking closely the theoretical carbon content of 20.40 per cent. The moisture was slightly low, ranging 32 to 33 per cent.

The magnesium was determined as magnesium pyrophosphate [$Mg_2P_2O_7$], following closely the U. S. P. X methods. (A trace of potassium was found, but not enough to determine quantitatively.) Aluminum and calcium were also tested for, but were not found to be



Characteristic Crystals of Tribasic Magnesium Citrate Obtained From Samples of Solution of Magnesium Citrate, One to Three Years Old.

present. The crystals which formed the deposit in the bottles were of the tri-clinic system, soluble in cold water with difficulty, but freely soluble in hot water. and the analyses seem to indicate the tri-basic magnesium citrate [$Mg_3(C_6H_5O_7)_2 \cdot 14\,H_2O$].

As a further interpretation of the results micro-photographs of these crystal deposits were taken. In a discussion of the composition of the salts formed in making magnesium citrate solution some authorities state (2) that the tribasic magnesium citrate is formed; [$Mg_3(C_6H_5O_7)_2$] others (3) say the dibasic acid salt [$MgHC_6H_5O_7$] magnesium acid citrate is formed. If $Mg_3(C_6H_5O_7)_2$ is formed, then approximately 11 to 13 grams of free citric acid would be present in excess per bottle. If $MgHC_6H_5O_7$ is the salt formed, only about one gram of citric acid would be in excess by the U. S. P. X formula. The U. S. P. X requires that free acid be present in the solution in sufficient quantity to neutralize 9.5 cc. N/2 alkali which, when calculated to citric acid, corresponds to about 3.32 per cent. or approximately 11.6 grams of free citric acid per bottle. It has also been claimed (4) that only the dibasic salt of magnesium citrate has therapeutic properties, while others disagree, and believe that it is the magnesium content only that is important and that it makes no difference which compound is present so long as magnesium is there in soluble form.

Again, in reference to the free acid content, where it has been claimed (5) that there is only about one gram of free acid present normally and that when titrating for free acid it is in reality the dibasic or acid salt that changes its composition with the alkali used and is thus read as an excess of free acid.

Up to the present time the dibasic salt of magnesium citrate seems to be known only theoretically. Repeated efforts on the part of the author to produce it by the usual methods have failed to yield this compound. What is the likelihood of its being present in the U. S. P. X solution of magnesium citrate? It will be noted that the free acid in samples two, three and four years old (see Table I) remained constant when analyzed according to the U. S. P. methods. Sixty-five per cent. of these samples contained a crystal deposit of the normal magnesium citrate, varying up to eight and one-half grams in weight. This would decrease the weight of magnesium acid citrate in the solution if it were present in this form, and when titrating for free acid as the U. S. P. X directs, if the acid were present, in the titration of such an abnormal sample the number of cc. of alkali used would be

diminished. This investigation shows that such is not the case, but that the acidity remains fairly constant in the samples containing crystal deposits; thereby disproving the old theories of a dibasic salt being present, because the results indicate that the alkali added by titration does not react with the compound in solution, but only with the free acid, which is present in excess, and that the compound formed is the tribasic salt of magnesium citrate.

From another viewpoint we can readily see that if the compound formed were the dibasic salt, then when it crystallized out of the solution, it would leave the solution much weaker in acid strength, and the amount of alkali used would be less, but it takes the same amount of alkali as if no precipitation had taken place, indicating that the alkali does not react with the compound in solution, but only with the free acid, and therefore if the free acid is present in the amount required by the U. S. P. X the compound formed must be the tribasic magnesium citrate.

In an effort to determine just what caused the deposit or sediment in samples of citrate after standing for a period of time varying from one week to three months, batches of citrate were made up following closely the U. S. P. X directions, but varying the amount of ingredients. As the results show, nothing definite was brought out by these experiments other than the fact that samples made without potassium bicarbonate did not produce sediment or crystal deposit, but developed molds, probably due to the free citric acid present. The other samples precipitated a crystalline deposit after standing for some time. The shortest time required for such precipitation was two weeks and the longest was three months.

Bottles of magnesium citrate containing crystalline deposits cannot be sold to the trade because of their abnormal appearance. It was found that by warming the bottles the solution of these crystals could be effected, depending upon the size of the crystals present, small crystals being more easily dissolved. The crystals can be dissolved by heating very slowly in a water bath kept at 50 degrees C. or slightly lower. Another method of redissolving the precipitate is to keep the bottles in a warm place, agitating them frequently. Care must be taken not to warm the bottles at too high a temperature. The increased pressure of the carbon dioxide present might possibly burst the bottles.

Samples of magnesium citrate were made with varying amounts of sugar and varying amounts of potassium bicarbonate, *i. e.*, one lot was made using 1.25 grams of $KHCO_3$ per bottle, and another with-

out any $KHCO_3$; the first lot developed a deposit within three months, but the one made without $KHCO_3$ did not develop a precipitate, but showed a mold growth at the end of three months.

Another set of preparations was made with an increase of 10 cc. per bottle of simple syrup, and one-half the quantity of $KHCO_3$ or 1.25 grams. This lot formed a precipitate within two and one-half months.

Another lot was made, decreasing the citric acid from 35 to 33 grams, using the regular amount of simple syrup and 1.25 grams of $KHCO_3$. This sample held up only three months. Another lot made with 33 grams citric acid, 70 cc. simple syrup and 1.25 grams $KHCO_3$ per bottle, remained perfectly clear for four months.

A table of the formulas used in making the experimental lots of magnesium citrate solution for this investigation is given below. Lot E held up the best, as stated above.

Ingredients	A	B	C	D	E	F	G
Magnesium Carbonate	15	15	15	15	15	15	15
Citric Acid	35	35	35	35	35	35	35
Simple syrup	60	60	70	70	70	60	75
Talc	5	5	5	5	5	5	5
Oil of lemon	1	1	1	1	1	1	1
$KHCO_3$	1.25	0	2.50	1.25	1.25	1.25	2.50

Following this series of experiments, a sample was made up following the U. S. P. X methods, but glucose was substituted as a sweetening agent for sugar. This lot did not hold up any longer than the regular U. S. P. samples. Another lot using saccharin was also made. These were started at room temperature and by the end of the month a deposit of crystals was formed.

These attempts to prepare a sample which would remain clear a reasonable length of time were not very successful, but several things can be deduced from these experiments: The U. S. P. X product as made by the retail pharmacist will remain from two to three months without becoming turbid; no mold growth will form if the U. S. P. X directions are followed closely; at the end of three months the product still has a good flavor. Also the amount of potassium bicarbonate used does not affect the stability of the solution, a precipitate forming both when small and large amounts were used. It should be noted, however, that no precipitate formed in samples that do not contain CO_2, but a mold growth. This demonstrates the inhibiting effects of CO_2 on mold growths.

Mr. Lee, of Lee Strauss Company, suggested that instead of using the regular amount of sugar in the solution of magnesium citrate, a larger amount be used in order to disguise the acidity and make the solution more agreeable. He suggested adding 7.5 grains more of sugar per bottle. Samples were made containing this amount and also samples containing 15 and 21.5 grains more of sucrose per bottle. In an organoleptic test conducted among four people, no one of the samples stood out as being more agreeable, showing the amount of sugar added was insufficient to make any noticeable difference in flavor. A much larger amount than that tried would be necessary to make the present formula yield a noticeably sweeter product.

The per cent. of sediment in the samples made by the U. S. P. IX method and the U. S. P. X method does not differ very much, indicating that the amount of citric acid does not make the preparation more stable. Samples made with 35 grains of citric acid showed a precipitate in the same length of time as did those made with 33 grains.

The percentage of sugar was determined in five of the samples and the results showed that the free citric acid had changed nearly all the sucrose present to invert sugar. The determinations were made according to the methods recommended in the Journal of the Association of the Official Agricultural Chemists, page 190, paragraph No. 35, 1925. Tabulated results from these determinations are as follows:

Date Analyzed	Sample #	Date Mfd.	Sucrose Before Inversion With HCl	Sugar After Inversion With HCl	Sucrose
4/10/28	3257	6/9/25	10.76	11.28	11.25
4/15/28	3684	10/27/25	11.00	12.36	12.29
4/20/28	3830	12/8/25	9.59	10.12	10.09
4/23/28	5081	2/15/27	13.60	14.12	14.09
4/25/28	5449	5/6/27	13.58	14.36	14.32
10/20/28	Mfd. in cold	24 hrs. old	trace	10.69	10.15
X Sample	Mfd. with heat	"	9.95	10.69	10.15

X sample is almost entirely inverted by citric acid after heating, as indicated by the U. S. P. X.

It is to be noted in the foregoing table that the sucrose used to make these preparations is almost entirely changed to invert sugar by the action of the free citric acid present. This inversion takes place in various degrees according to the method of making the preparations and the time they are allowed to stand. Some of the samples upon which determinations were made were several years old at the time of the analysis. In order to ascertain the length of time necessary for the sucrose to invert, several additional experiments were performed.

It was found that if the U. S. P. X method was followed closely, especially directions for bringing the preparation to the boiling point, inversion began at once and within twenty-four hours the sucrose was entirely changed to invert sugar. If the preparation was not heated, but made at room temperature, then the inversion proceeded very slowly and a much longer period of time was needed to change the sucrose to invert sugar.

A 10 per cent. sugar solution was made, with 3.325 per cent. of citric acid, so as to resemble a sample of citrate containing the average amount of free citric acid. This was done to determine whether the acid inverted the sugar as quickly as in the U. S. P. X samples. One part of this solution was brought to the boiling point as directed in the U. S. P. X; the other was allowed to stand as originally made. In twenty-four hours the sucrose in the sample which had been heated was almost entirely changed to invert sugar, as was the sucrose in the U. S. P. X sample under the same conditions. The sample that was allowed to remain at room temperature showed only a trace of the action of the citric acid; this also paralleled the case of the unheated U. S. P. X sample. Although this experiment does not prove anything definite, it does show clearly the relation between the U. S. P. X solution of citrate of magnesium and a sugar solution containing citric acid in the same proportion as it is present in the U. S. P. X formula. The action of the acid on the sugar content of these two similar samples is another confirmation of the belief that the U. S. P. X solution of magnesium citrate contains free citric acid and not magnesium acid citrate.

Below is a table of the compensation of magnesium citrate solution according to a number of foreign pharmacopœias, showing the citric acid and magnesium carbonate content in comparison with that found in the U. S. P. X.

	Citric Acid in grams	$MgCO_3$	*Ratio Citric Acid to* $MgCO_3$
U. S. P. X	35	15	2.33 : 1
Swiss	35	20	1.75 : 1
French	32	20	1.60 : 1
Belgium	30	18	1.66 : 1
Italian	20	12	1.66 : 1
Dutch	15	10	1.50 : 1
Mexican	36	24	1.50 : 1

From the above figures it may be seen that the foreign pharmacopœias base their figures on the assumption that neutral tribasic citrate of magnesia is formed. This has a ratio of 1.44 grams of citric acid to 1 gram of $MgCO_3$, while the dibasic compound has a ratio of 2.16 grams of citric acid to 1 gram of $MgCO_3$.

Conclusions

The analyses of the crystalline deposit in deteriorated samples of solution of magnesium citrate indicate that the neutral tribasic compound of magnesium is present having the formula $Mg_3(C_6H_5O_7)_2 .14\ H_2O$.

The analyses of samples of citrate of magnesium solution varying in age from one to three years verifies the fact that the tribasic magnesium citrate is the compound formed in the solution of citrate of magnesium as directed in the U. S. P. X.

Of the various formulas tried in an attempt to prepare a permanently clear solution of citrate, none were successful, but if the U. S. P. X directions are followed closely, a fairly stable product is formed, remaining clear three months.

The presence of carbon dioxide in the samples is an important factor in reducing mold growth and the stability of the solution is dependent upon it.

The foreign pharmacopœias base the formulas for the manufacture of solution of citrate of magnesium on the assumption that tribasic compound of magnesium citrate is formed.

The majority of the samples of magnesium citrate solution obtained on the market did not meet the U. S. P. requirements.

Samples of magnesium citrate solution containing crystal deposits may be restored to their normal condition by warming and agitating at a properly controlled temperature.

The sugar in samples of magnesium citrate is inverted under the same conditions as a plain sugar solution containing the same amount of free acid, indicating that the U. S. P. X samples contain free citric acid and not magnesium acid citrate.

TABLE I

	No.	Date Mfd.	Character of Sample	U. S. P. Requirements 9.5 cc. N/2 Alkali for 10 cc. U. S. P. Minimum Free Acidity Test	3.32 Free Acid as Citric	28 cc. Total cc. N/2 Acid for U. S. P. Minimum Total Acid Test	9.8 Total Organic Acid as Citric	0.414 gm. $Mg_2P_2O_7$ in 10 cc.	1.5 gms. MgO in 100 cc.
1	2618	12-9-24	Crystals present	10.66	3.78	21.80	7.63	.2645	.957
2	2883	2-23-25	Few " "	10.48	3.66	25.84	9.04	.400	1.45
3	2893	2-26-25	Present	10.24	3.58	22.30	7.80	.3125	1.13
4	2902	3-2-25	"	10.12	3.54	23.02	8.05	.338	1.22
5	2957	3-7-25	"	10.06	3.51	22.86	8.00	.361	1.30
6	3051	4-3-25	Few " "	11.74	4.10	26.91	9.41	.400	1.45
7	3073	4-10-25	Few "	10.06	3.52	21.76	7.59	.367	1.33
8	3089	4-17-25	Few "	11.65	4.07	23.09	8.08	.357	1.29
9	3257	6-9-25	Few "	10.09	3.53	23.42	8.19	.390	1.41
10	3302	6-25-25	Few "	11.86	4.15	21.80	7.63	.3865	1.39
11	3560	9-15-25	No crystals	11.50	4.02	26.25	9.18	.419	1.52
12	3684	10-27-25	Present	11.05	3.86	24.02	8.40	.379	1.37
13	3830	12-8-25	No crystals	12.93	4.52	27.04	9.46	.358	1.296
14	4019	2-9-26	Few "	11.84	4.14	26.58	9.30	.3795	1.376
15	4076	2-23-26	No "	11.14	3.90	28.69	10.04	.392	1.42
16	4183	3-30-26	Few "	12.39	4.33	27.00	9.45	.383	1.386
17	4283	4-21-26	No "	11.66	4.08	27.72	9.70	.397	1.43
18	4448	7-8-26	Few "	11.99	4.19	25.75	9.00	.4085	1.48
19	4721	10-14-26	Few "	13.62	4.76	25.30	8.85	.403	1.459
20	5017	1-27-27	No "	12.71	4.44	28.10	9.83	.4005	1.45
21	5081	2-15-27	Crystals	9.27	3.24	24.03	8.40	.355	1.285
22	5232	3-23-27	No "	12.97	4.53	28.61	10.01	.392	1.42
23	5449	5-6-27	No "	12.36	4.22	29.00	10.15	.422	1.53
24	5576	5-31-27	No "	12.78	4.47	29.75	10.41	.4165	1.51
25	5681	6-29-27	No "	12.94	4.52	29.81	10.43	.407	1.47
26	5881	8-30-27	No "	12.02	4.20	29.80	10.42	.414	1.50

TABLE 2

27	1928	No	"	10.18	3.56	29.50	10.32	.506	1.83
28	1928	No	"	6.70	2.34	20.00	7.00	.400	1.45
29	1928	No	"	9.50	3.32	29.00	10.15	.480	1.73
30	1928	No	"	8.75	3.05	27.20	9.52	.490	1.78
31	1928	No	"	11.20	3.92	27.20	9.52	.432	1.59
32	1928	No	"	7.20	2.47	25.60	8.96	.483	1.76
33	1928	No	"	7.20	2.47	23.50	8.08	.401	1.46
34	1928	No	"	6.90	2.41	22.40	7.84	.385	1.40
35	1928	No	"	6.50	2.24	21.50	7.52	.390	1.42
36	1928	No	"	6.9	2.41	22.90	8.01	.410	1.49
37	1928	No	"	6.07	2.12	23.00	8.05	.475	1.73
38	1928	No	"	7.10	2.47	25.50	8.92	.492	1.79
39	1928	No	"	5.75	2.01	24.10	8.44	.470	1.71
40	1928	No	"	6.95	2.43	24.70	8.64	.486	1.77
41	1928	No	"	6.95	2.43	22.70	7.94	.404	1.47
42	1928	No	"	7.00	2.45	25.75	9.01	.495	1.80

A CRITICAL STUDY OF METHODS OF ASSAY OF CHLORAL HYDRATE*

By H. A. Watson

University of Manitoba, Winnipeg, Manitoba

On account of the number of methods introduced for determining chloral hydrate quantitatively, many of which have appeared, to some degree, unsatisfactory, a study of the most important of them has been undertaken. The principal object was to find a satisfactory method of determining this substance in organs and tissues, and hence this phase of the investigation has been given somewhat more attention. A comparison has been made between the results obtained by various methods, using aliquot parts of a carefully prepared solution for each test.

The methods examined fall into the following classes:

(1) Chloral hydrate is treated with caustic alkali, and the formic acid produced determined by titration.

(2) The formic acid produced as above is estimated by the reduction of mercuric to mercurous chloride.

(3) Magnesium oxide is used to break up the chloral hydrate, and the formic acid produced is determined by the reduction of mercuric to mercurous chloride.

(4) The chloroform liberated by magnesium oxide as above is estimated.

(5) The chloral hydrate is converted into chloride by alcoholic alkali.

(6) The conversion to chloride is performed with zinc dust.

(7) Methods of assay using standard iodine solution.

Discussion of Methods

Class (1).

Since chloral hydrate is readily acted upon by excess of caustic alkali, giving as reaction products, chloroform and alkaline formate, according to the equation:

*The work herein recorded was included in a thesis presented in part fulfilment of the requirements for the degree of M. Sc. of the University of Manitoba.

$CCl_3CH(OH)_2 + KOH \longrightarrow CHCl_3 + H.COOK + H_2O$.....(1)
a method of determination is based on the amount of alkali used in neutralising the formic acid produced.

As is well known, however, the chloroform resulting from the above reaction is attacked by the alkali present to a varying degree, depending on conditions, a further quantity of alkali being used up for this purpose.

In the cold, the reaction appears to be mainly as follows:

$$CHCl_3 + 3KOH \longrightarrow 3KCl + CO + 2H_2O \text{.....(2)}$$

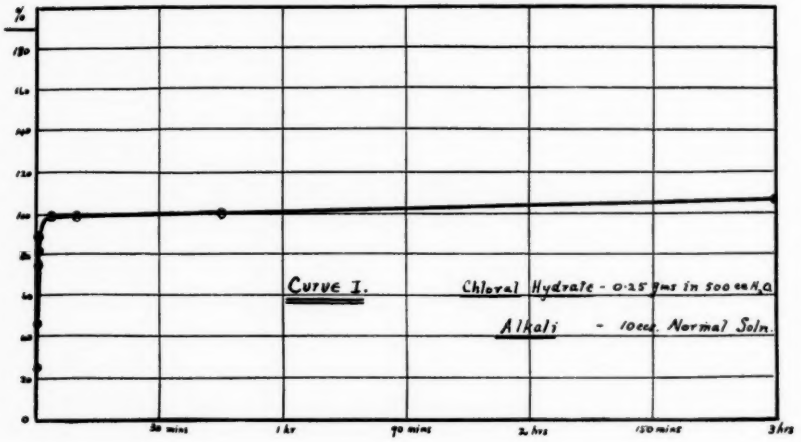
alkali being consumed in the formation of chloride. If boiled, besides chloride a further quantity of formic acid, in excess of that required by Equation (1) is produced, as follows:

$$CHCl_3 + 4KOH \longrightarrow 3KCl + H.COOK + 2H_2O \text{....(3)}$$

Thiele and Dent [1] have shown that up to 66% of the chloroform is capable of conversion to formate in this way under especially favorable conditions. The writer confirmed the presence of formate qualitatively. Various authors have suggested a modified technique to overcome this undesirable interaction of the alkali and the chloroform. Hinrichs [2] suggests using half-normal alkali and allowing contact only for two minutes, then titrating back with standard acid. Self [3] observes no care as to length of contact of the alkali, or as to temperature, but applies a correction based on a determination of the chloride formed during the course of the reaction. Garnier [4] suggests using a small excess of tenth-normal alkali for 15 to 20 minutes at 15° C. or less. Various other differences in time, strength of alkali, etc., are given by Bourdet,[5] Alcock and Thomas,[6] Sergeant,[7] Francois,[8] and Andron,[9] to overcome the difficulty.

To obtain satisfactory results by this method, it is obvious that conditions must be such that the reaction represented by Equation (1) is completed, and that those represented by Equations (2) and (3) have not started or are at a minimum, neglecting for the present the method of measuring the extent to which these have taken place. By conducting the test in the cold, Equation (3) may be eliminated, and the comparative rates of the two other reactions studied by allowing contact of the chloral hydrate with alkali for varying lengths of time. This reaction was plotted, it being found necessary to use a dilute reaction mixture in order to secure data for the whole curve, the first action being so very rapid. The curve obtained is given below.

A solution of 0.25 gms. chloral hydrate in 500 cc. of water at room temperature was treated with 10 cc. of normal alkali. At four minutes the primary reaction appeared to be complete. At ten minutes, this value was not measurably increased, and from a study of the curve a still longer contact might be made without the effect of the secondary reaction becoming noticeable.



Curve showing Decomposition of Chloral Hydrate.

Curve I

No special mention is made in the literature to use a dilute solution for the test, and yet the curve would indicate that the interference of the secondary reaction is best regulated by this means. It is to be noted that such a method could not be applied to distillates of chloral hydrate of unknown dilution, but might very well be used in the assay of crystals. Owing to its limited value and to its unsuitability for assaying small amounts of chloral in organs and tissues, it was not investigated further at this time.

Before leaving this method it might be well to indicate what results were obtained, using Self's [3] method of correcting for chloride formed. The details of the test are as follows: 25 cc. of 1% chloral hydrate solution was allowed to stand with 30 cc. tenth-normal alkali for twelve hours at room temperature. The usual titration was performed with acid, and the chloride present determined, allowing for traces of chloride present in the reagents. On applying the chloride

correction a value of 99.5% was obtained which agrees with the results given by the other methods. Without the correction the value was 103.2%. Another test was now made, similar in every way to the above, except that the reaction mixture was raised slowly to boiling, then cooled and titrated. On determining the chloride produced, and making proper allowance for its formation, a high result was obtained (101.96%), showing that, under these conditions, the single correction for chloride is insufficient.

Class (2).

A second method of determining the formic acid produced by the action of alkali on chloral hydrate, and one which, being gravimetric, is more accurate for the purpose desired, is by the reduction of mercuric to mercurous chloride. Since this method does not measure acidity, as such, but only formic acid, a longer contact between the alkali and the chloroform, if in the cold, and conforming therefore to Equation (2), would not affect the result as it would have done in the last method. Also, since the reactions expressed by Equation (3) do not come into play when the mixture is cold. they need not be considered either. We have here, then, a good method for determining accurately small amounts of chloral, and one which Archangelsky [10] uses for determining this substance in organs and tissues. Unfortunately, the distillate containing the substance is directed by him to be *evaporated down in the presence of free alkali.* This has been shown to produce an increased quantity of formic acid, and the high results obtained in the course of this investigation give ample confirmation of the necessity for a modified procedure at this point.

The following method of reducing the volume of bulky distillates was adopted to avoid introducing this error. Each portion of 700-800 cc. of distillate, obtained by steam distillation according to the method, is treated with 30-50 cc. of normal caustic alkali for 10-15 minutes *in the cold,* with occasional stirring, and then neutralized with normal HCl, using azolitmin indicator. After adding about three drops of acid in excess, about one decigramme of finely precipitated calcium carbonate is added and stirred until the indicator shows that the solution is neutral. The liquid is now filtered and evaporated down to small volume, washed into a graduated flask, and a few drops of acid added to dissolve traces of carbonate. When all the portions of distillate have been so treated and washed into the graduated flask, the con-

tents are made up to the mark, and aliquot parts taken for the precipitation with mercuric chloride. Adopting the method of Archangelsky without the foregoing modification, and omitting any distillation, various high and erratic results were obtained, as follows: 150.5; 148.5; 131.0; 142.0; 117.3; 113.8; 107.0; 99.7%.† The modified procedure just outlined, gave results on similar solutions of 99.04%; 98.72%, the sample used being considered, from a comparison of all the methods, to be 99.5% pure. Further results, obtained by this modified method, but after subjecting weighed quantities of chloral hydrate to steam distillation in the manner described in the next section, were found to be 98.0 and 98.1%, which, assuming the purity of 99.5%, is about 1½% low.

These results, it will be seen, are much nearer the correct values and are more consistent among themselves, than those obtained by Archangelsky's method.

Some further work was done to try to find out why the loss was fairly constant around 1%, even when the pure solution was evaporated down and the distillation omitted. It was thought that it might be either a loss of formic acid by hydrolysis and evaporation, or a decomposition of formate as described under the section in which magnesium oxide is used. A solution of formic acid, whose strength was exactly determined by reduction of mercuric chloride, was neutralized with sodium hydroxide and diluted to 700-800 cc. It was then evaporated down to small volume and a loss of 0.86% was recorded, which was not so recorded when the mixture was refluxed for a long time. This would rather indicate a partial hydrolysis and a slight loss of formic acid, and not a decomposition of the formate. A further test, conducted with the same formic acid solution, and following the modified Archangelsky procedure, showed a loss of 1.3% in the amount of formic acid recovered.

It would seem, therefore, impossible by any ordinary means to improve the accuracy of the method any further, since the bulky distillates must, of necessity, be reduced to small volume before the addition of the mercuric chloride solution.

The time required to remove chloral hydrate from organs by Archangelsky's steam distillation method was also examined. It is stated that the distillation should be continued for from 12-20 hours.

†This sample was warmed on the water bath, shut off for the night and continued the next day. The chloroform may have escaped at a comparatively low temperature.

A pure solution was first examined as follows: A steam distillation of a solution of 2 gms. of chloral hydrate in 500 cc. of water, with an equal weight of 20% phosphoric acid, was carried out, each 100 cc. of distillate being collected up to 1500 cc. Then each 500 cc. was collected up to a total of 3½ litres. Further amounts of distillate gave unweighable quantities of mercurous chloride on reduction. The total time taken for the collection of the 3½ litres of distillate was about 8½ hours, and the quantities recovered, using the modified method of assay are given below.

1st	100 cc.	0.4764
2nd	100 cc.	.3558
3rd	100 cc.	.2718
4th	100 cc.	.2074
5th	100 cc.	.1569
6th	100 cc.	.1210
7th	100 cc.	.0885
8th	100 cc.	.0717
9th	100 cc.	.0551
10th	100 cc.	.0413
11th	100 cc.	.0288
12th	100 cc.	.0224
13th	100 cc.	.0163
14th	100 cc.	.0115
15th	100 cc.	.0081
1500 cc.		1.9330 gms.

500 cc. portions.

1st	500 cc.	1.4683
2nd	500 cc.	.3776
3rd	500 cc.	.0871
4th	500 cc.	.0230
5th	500 cc.	.0048
6th	500 cc.	.0009
7th	500 cc.	.0003
3500 cc.		1.9620 gms.

equivalent to *98.1%* recovery.

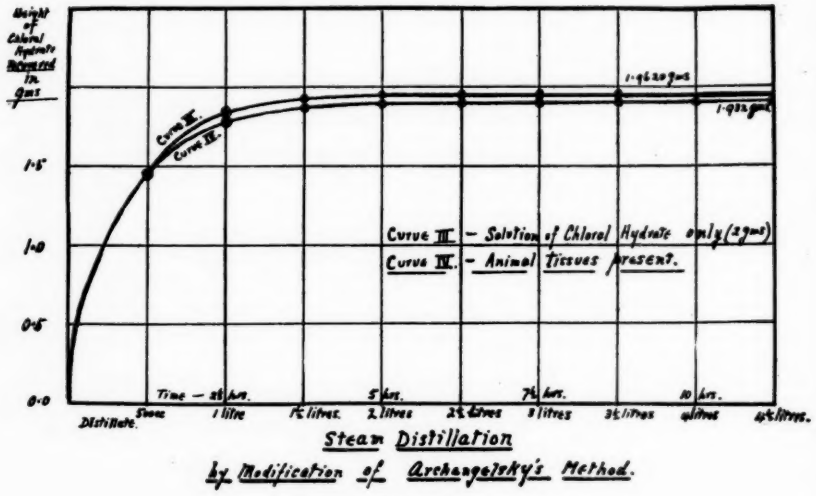
A similar distillation to check the amount recovered, and evaporating all the distillates to a known volume, of which an aliquot part was then taken, yielded, when 4 gms. of chloral hydrate was taken, 3.918 gms., corresponding to a recovery of 98.0%, which is practically the same as in the last case.

A third distillation was then made, duplicating the first one except that the chloral hydrate solution was thoroughly ground up with sausage meat and allowed to stand overnight before distilling. In this case the chloral hydrate appeared to be liberated somewhat more slowly, and the yield was slightly lower. The amounts recovered, using, as before, the modified method of assay, were as follows:

1st	500 cc.	1.4610 gms.
2nd	500 cc.	.3160
3rd	500 cc.	.0943
4th	500 cc.	.0313
5th	500 cc.	.0108
6th	500 cc.	.0062
7th	500 cc.	.0052
8th	500 cc.	.0038
9th	500 cc.	.0033
4½ litres		1.9319 gms.

equivalent to recovery of *96.59%*

In this case, 4½ litres was distilled off, and the time required was about 11½ hours. These results are shown graphically in Curves III and IV.



Curves III and IV

As regards the time of distillation then, it would seem as though 11-12 hours would remove all but traces. It seems advisable, however, to continue the distillation until the last portion of the distillate gives an unweighable amount of mercurous chloride on reduction.

In view of the findings here recorded, it also seems advisable to adopt the suggested modification, since the results are shown to be more reliable.

It should be mentioned here that, although Thiele & Dent [1] found formic acid to be produced between chloroform and alkali, even at ordinary temperatures (25° C.), the conditions set up by them were made extremely favorable. The alkali was very strong in comparison, a centrifugal stirrer was employed, and the action carried on for several hours. In the modified procedure here recommended, the concentration of alkali, at the moment of addition, is about one-fifth of one per cent., whereas that used by the aforementioned experimenters, at this temperature, was about 22%. Further, the time suggested for contact with the alkali is 10-15 minutes, as against 3-4 hours given by them.

To determine, therefore, what error, if any, is introduced under ordinary conditions, due to the above reaction, several tests were made, the details of which follow: 25 cc. of 1% chloral hydrate solution were treated with 30 cc. tenth normal alkali for a few minutes, and for 12 hours at room temperature. The difference between the two values obtained was within the experimental error. Another test using a mixture of formic acid of known strength, and the proper proportion of chloroform, diluted and treated as suggested under the modified procedure gave no increased amount of formic acid over that known to be present, allowing the stated contact with alkali of 10-15 minutes.

These tests serve to show that the assumption that no formic acid is produced in the cold when alkali and chloroform react, is practically correct under the conditions stated.

Class (3).

Another method of splitting up chloral hydrate into formate and chloroform, is by boiling with magnesium oxide, instead of by treatment with caustic alkali. The formic acid then liberated is determined by the reduction of mercuric to mercurous chloride.

Owing to the weaker basic properties and the greater insolubility of this alkali, it has been thought that by its use, the interference of the reaction expressed by Equation (3) might be eliminated. Actual experiments to see if chloroform and magnesium oxide reacted to produce any formic acid, gave negative results. The above method then, which appears in *Fuller's Chemistry and Analysis of Drugs and Medicines,* appeared at first glance as though it would be an excellent one. The chloral solution was refluxed until decomposed, the excess of magnesium oxide dissolved in hydrochloric acid or

filtered off, and the formic acid determined. Results were consistently low after several trials. Tests were made to ensure complete decomposition of the chloral hydrate, to guard against loss from the reflux condenser, etc., different amounts of magnesium oxide were taken and the refluxing carried on for varying lengths of time. Results from 7 to 15% low were obtained. Coming finally to the conclusion that magnesium formate may be partly unstable at the boiling temperature, and seeing statements by Kunz-Krause and Manicke [11] to this effect, a test was made to see if such were the case. Formic acid of known strength was refluxed with magnesium oxide, and then determined as usual by the mercuric chloride reduction. The amount recovered was only 93.9%.

By treating chloral hydrate solutions in the cold with magnesium oxide overnight, higher results were obtained, but since the reduction with mercuric chloride solution is, of necessity, carried on at the boiling temperature, and is a comparatively slow reaction, some decomposition of magnesium formate may take place even by this method. From the results obtained, which were still from 2 to 3% low, this seems very probable.

From the values obtained, therefore, it would seem that the above method of assay, using magnesium oxide, is unreliable.

Class (4).

In this method, the chloroform liberated by boiling with magnesium oxide, is determined.

Rosenthaler and Reis [12] state that although they observed no action between chloroform and magnesium oxide, nevertheless, when chloral hydrate was boiled with this oxide, a secondary reaction took place, whereby carbon monoxide and magnesium chloride were formed, with consequent loss of chloroform. The above method without modification, therefore, might be expected to give low results on account of this loss.

Kippenberger's [13] method is based on an attempt to overcome this loss of chloroform by a determination of the amount of carbon monoxide evolved according to the equation:

$$CHCl_3 + 3KOH \longrightarrow 3KCl + 2H_2O + CO.$$

His method is briefly as follows: The material to be tested is examined with litmus and made slightly acid. MgO is then added, and the whole distilled in the ordinary way into a Woulff's bottle.

The second neck of this bottle is connected to a wash bottle containing HCl, and then to a ten-bulb Lunge absorption apparatus containing palladium chloride, which is kept warm by means of a bath of warm water. Air is aspirated through the apparatus until the $CHCl_3$ is all over and the CO has been absorbed into the palladium chloride. Any liquid $CHCl_3$ collected in the Woulff's bottle is separated in a separatory funnel, and weighed directly. The aqueous liquid, containing dissolved $CHCl_3$ is treated by Vortmann's method, a procedure using potassium permanganate and iodine. To these two quantities, is added the amount of $CHCl_3$ corresponding to the reduced palladium. The following are results reported by Kippenberger:

(1)	(2)	(3)	(4)	(5)	(6)	(7)
Chloral Hyd. used	Liq. $CHCl_3$	Dis'lvd $CHCl_3$	CO	% recovered	% left in dist. flask	% unaccounted for
gms.	Calc. as Chloral Hyd. gms.					
5.0	3.8006	0.2601	0.0115	81.4	10.9	7.7
10.0	8.9131	0.2522	0.0415	92.1	4.5	3.4
10.0	9.0507	0.4312	0.0328	95.1	2.1	2.8

The volume of liquid decreases from 300 cc. in the first of the above to 200 cc. in the second, and the last has only 120 cc.

From a study of the above figures, several points may be noticed. A considerable loss which is unaccounted for, is shown in Column 7. This, it is explained, is by loss of chloroform from the use of rubber connections. Another loss is the considerable quantity of $CHCl_3$ which is found at the termination of the test in the distillation flask. Column 6. These two amounts reduce the percentage of recovered material considerably, as will be seen from Column 5, and the greater the volume of liquid present at the beginning, the greater the loss, it would seem.

A very interesting point, however, is in connection with the small amount of palladium recovered. In a preliminary experiment, Kippenberger shows that, after distillation of 5 gms. of chloral hydrate in 200 cc. of water, with 10 gms. of MgO, the amount of chloride left in the flask corresponds to a decomposition of 6.27% of the chloral hydrate taken. In a later distillation, using the CO absorption method, and almost exactly similar quantities of materials the correction for decomposed chlorate hydrate is only .23%. In two other distillations

with varying amounts of materials the corrections are .415% and .328% respectively. The amount of chloral hydrate calculated from the recovered palladium is only a small fraction of what would be expected from the amount of chloride known to be formed in the single experiment. How can this difference be explained? The equation may not be as simple as that suggested by Kippenberger. The equations given by Kunz-Krause and Manicke, at any rate suggest that it may be fairly complex. A correct interpretation of the reactions involved would probably explain the values given in Column 7 of the table, as unaccounted for.

A rather serious objection to the measurement of the CO evolved, as a measure of the $CHCl_3$ decomposed to chloride, arises if the work of Kunz-Krause and Manicke be considered in this connection. They have shown, as indicated earlier, that magnesium formate partly decomposes when boiled, giving CO and CO_2. Thus, a part of the absorbed CO in Kippenberger's experiments may have been from this source and *not from the $CHCl_3$ at all,* since magnesium formate is present in the distillation flask, and may be decomposed as indicated.

The whole principle of Kippenberger's method, then, appears to be open to serious objection.

Class (5).

The chloral hydrate is converted to chloride by alcoholic alkali.

Since the time of Dumas it has been known that boiling alcoholic potash attacks chloroform according to the equation:

$$CHCl_3 + 4KOH \longrightarrow 3KCl + H.COOK + 2H_2O.$$

Since chloral hydrate is readily converted under the circumstances of the test to chloroform, chloral hydrate will also undergo this change, and it may be assayed by this method.

As the reaction is accompanied by the formation of certain volatile substances including organic chlorides, such as carbonyl chloride, according to Prunier and Mossler,[14] the conversion of all the chloroform to KCl is incomplete when heated under a reflux condenser. A. V. Harcourt[15] states that results depending on this reaction are a few per cent. too low. Nicloux[16] gives the values 1.5 to 2.0% low as a constant error. M. Berthelot[17] states that all the chlorine does not combine with the potassium. In the present study an error of several per cent. was found when the mixture was refluxed, but by using

a pressure bottle, and observing certain precautions, quite good results may be obtained.

Various writers, amongst whom are L. de St. Martin,[18] Pückner,[19] Putt,[20] Sasse,[21] Murray [22] and Moraw,[23] Kolthoff,[24] Willgerodt,[25] Dowzard,[26] Russwürm,[27] Nicloux,[16] Wallis,[28] Chancel and Parmentier,[29] have used either one form or the other. Nicloux [16] determines chloroform in amounts from 0.1 to 0.004 gms. by heating for one hour in a reflux apparatus 60 cc. of alcohol containing the chloroform, with 10 cc. of 10% alcoholic KOH, then estimating the chloride. This was the method, in general, used in this work, substituting chloral hydrate for the chloroform.

Following this method, but continuing the refluxing for 3-4 hours, gave a result of 96.85%. Two other results obtained by one hour refluxing, were 96.23 and 95.31% respectively.

Wallis [28] in trying to work out a satisfactory method of determination, decided from a consideration of the work of Chancel and Parmentier,[29] to use a closed vessel with alcoholic caustic soda for three hours.

This method is stated exactly, since it was the one used when making this type of conversion in a bottle under pressure. 0.1 gms. of chloral hydrate in 10 cc. alcohol, is treated with 10 cc. of normal aqueous soda in a small glass bottle. A rubber stopper is tied securely into the neck of the bottle, which is heated for three hours in the boiling water-bath. On cooling and opening the bottle, the chlorine content of the liquid is determined by precipitation with $AgNO_3$, from nitric acid solution, or by titration. Wallis found that the best results were obtained when the alcoholic alkali was equal to about 50% by volume of alcohol, and with this strength, he obtained a series of results 99.47, 99.3, 99.4, 99.3%.

The results here recorded were obtained in a round-bottomed Jena glass flask with rather small neck which was easily corked and tied, and a mean value of 99.63% was obtained.

In connection with this method, it is of interest to note that Bettink and Van den Driessen Marreeuw,[30] in examining organs for chloral hydrate, adopted this type of conversion, after finding that the methods of Archangelsky [10] and Kippenberger [13] gave divergent values. From what has been said of the two latter methods, it seems only to be expected that results obtained by them should differ.

The low values obtained by refluxing with alcoholic alkali, and the reasons for them, have also been indicated.

Class (*6*).

Conversion of chloral hydrate to chloride by means of zinc dust.

After observing a statement in Watt's Dictionary that chloral hydrate, when boiled with zinc dust is decomposed to zinc chloride and oxychloride, Self [3] suggested this, and a subsequent determination of chloride, as a method of assay of chloral hydrate.

The method suggested by him is as follows: 0.3 gms. of chloral hydrate in 60 cc. of water is treated with 2 gms. of zinc dust for 20 minutes under a reflux condenser. Ten cc. of acetic acid are now added, and after two minutes, the clear liquid is filtered from the zinc, and the chloride determined.

Results obtained by this method were found to be about 15% low, but this was due merely to incompleteness of the reaction in the time given by Self. Acetic acid is directed to be added after the boiling, allowing it to stand for two minutes, and then filtered from the excess zinc. There seems to be no object in conducting the test this way for, in two minutes, there is manifestly little reduction effected. To ensure completion of the reaction, the acid was added at the beginning, and the refluxing carried on for 1½ hours. A mean result of 99.89 was then obtained.

Since zinc dust sometimes contains small amounts of chloride, as pointed out by Self, it is well to conduct a blank determination.

This method of conversion by means of zinc is quick and clean, there is no etching of the glass, and no scaly precipitate occurs as in the alkaline conversion. In addition, the results obtained are more exact than those resulting from the use of alcoholic alkali under a reflux. It should be remembered, however, when determining chloral hydrate as chloride, that certain organs such as the stomach may contain free hydrochloric acid.

Class (*7*).

Methods of assay depending on the use of a solution of iodine.

A method suggested by Rupp [31] depends on the oxidising action of a solution of hypoiodous acid produced by mixing iodine solution and alkali. The action may be represented as follows:

$$CCl_3CH(OH)_2 + 2I + 2KOH \longrightarrow 2KI + 2H_2O + CO_2 + CHCl_3.$$

The method is briefly stated as follows: Take 10 cc. of 1% chloral hydrate solution and place for 10 minutes in a stoppered bottle with a

mixture of 2.5 cc. of normal KOH solution. Then dilute with 50 cc. of water, add 5 cc. HCl (sp. gr. 1.125) and titrate the liberated iodine with tenth normal thiosulphate. One cc. iodine = 0.00827 gms. chloral hydrate.

It was later suggested by Rupp,[81] that this method gave good results only if the iodine were added to the chloral hydrate first, and the alkali added afterwards.

The action of alkali and chloral hydrate has been already indicated. (Equation (1) earlier in this report.) The action is quite rapid, and the first products, at any rate, are alkaline formate and chloroform. This reaction appears to be an interfering secondary reaction in the iodometric method, and is the probable reason for its failure to give exact results if the alkali is not added last.

From certain results obtained in a study of this method, however, it would seem that even if the alkali is added last, this interaction between it and the chloral hydrate is not wholly prevented, using the concentrations indicated by Rupp. About 97.0% was the best value obtained, following the method exactly as described, and this value is confirmed by Wallis [28] who could get no better result. It was found further, that the manner of adding the alkali affected the results. Pouring in the stated amount of alkali from a pipette, without stirring during the addition, gave a result of about 95%. By pouring in the alkali drop by drop, with constant shaking, an average value of 98.8% was obtained. It seemed, then, that if this secondary reaction could be reduced to a minimum, or, if possible, entirely eliminated, still better results might be obtained. The most likely way seemed to be to dilute the alkali considerably, and then make the addition very slowly, drop by drop, with constant shaking. A value averaging 99.5% was obtained when this was done, using 25 cc. of tenth normal alkali instead of 2.5 cc. of normal alkali, this result being about the correct value for the sample used. It was therefore considered that the results could not, probably, be improved any more, and it is suggested that the method be adopted with the foregoing change. The suitability of the method for large volumes of distillates was tried out by taking a very much diluted sample of chloral hydrate. By taking the precautions indicated, a good result was obtained (99.6%).

Kolthoff [24] recommends the following method: To 25 cc. tenth normal iodine solution, add 10 cc. of twice normal caustic soda and 10 cc. of tenth normal solution of chloral hydrate. Stopper and stand

one hour. Acidify with dilute HCl and titrate the excess of iodine with thiosulphate solution. Adding these in the order named, a result of only 36.4% was obtained by the writer. Modifying this by adding the alkali last, results of 59.1 and 62.4% were obtained. The reason for the uncertain results is probably the same as in the method of Rupp, the error being accentuated by the use of a stronger solution, and a larger quantity of alkali.

Comparison of the Results Obtained by Using the Various Methods

A series of experiments was made to compare the results obtainable by the various methods. For these, an accurately prepared 1% solution of chloral hydrate, which was kept cool, was used, the time elapsing during the series of tests being kept as short as possible.

For a comparison such as this, it was not found practicable, employing Method (1) to use a volumetric solution as strong as normal or half-normal, but Garnier's method using tenth normal alkali was adopted. Even with this strength of alkali, an increased amount of chloral hydrate solution (25 cc. instead of 10 cc.) was used, in order to minimise the experimental error. The temperature was kept at a little below 15° C. for 20 minutes, according to the method, and only the slightest excess of alkali over that required for the reaction was used. The chloral hydrate solution was made exactly neutral before commencing. The results obtained are given in the appended table, Column 2.

Similar tests made at room temperature, using 30 cc. tenth normal alkali for 10 minutes, gave better results which are given in Column 1.

Employing Method 2, the preliminary conversion to formic acid by alkali was performed in different ways. In one case 10 cc. of normal alkali reacted with 25 cc. of 1% chloral hydrate solution for 3-4 minutes, in the cold, after which it was acidified slightly and the mercuric chloride added with consequent reduction to mercurous chloride. Two results were 99.36 and 99.44%. In a second, the time of reaction was increased to 20-25 mins. and a result of 99.40% was obtained. In the third case, 30 cc. of tenth normal alkali reacted at 25° C. for 20-25 mins., and a result of 99.40% was obtained. These results are recorded in Column 3, and serve to bear out the earlier statement that at ordinary temperatures the effect of Equation (3) is negligible.

When the reaction between alkali and chloral hydrate is allowed to proceed at boiling temperature, as is the case in Archangelsky's method, high and erratic results are obtained as shown in Column 5. The first value, 99.73% was obtained as follows: The reacting mixture of 2 gms. chloral hydrate in 500 cc. water with 40 cc. N-soda, was heated and the water bath then shut off for the night. Next morning the evaporation was resumed. The second value of 107.0% was obtained by repeating the above exactly, except that the mixture was brought rather rapidly to the boil, and the evaporation then continued without interruption. The next three results 150.5-148.5-131-0% were obtained using the special solution, 25 cc. of which were diluted to 725 cc. with water, 30 cc. of N-soda were added and the whole evaporated on the water bath to 30-50 cc. This was then neutralized with acetic acid (free from formic acid), an equal volume of saturated mercuric chloride solution added, and the whole precipitated on the water bath for several hours, this being the procedure given by Archangelsky.

The modified procedure described earlier, to overcome the action of the alkali on the chloroform during evaporation, gave results on the special solution of 99.04 and 98.72% given in Column 4.

Method (3) in which the splitting up of the chloral is effected by refluxing with MgO, has been shown to give low results in every case. Results obtained on the special solution were 92.88 and 92.40%, given in Column 6, and by allowing to stand overnight with MgO instead of refluxing, results of 96.84 and 97.80% were obtained (Column 7).

Method (5) gave for this series, values of 96.23 : 95.31%, when refluxed, given in Column 8, but when the closed bottle was used, better values were obtained as follows: 99.54-99.84-99.77-99.38%. These are shown in Column 9.

As before indicated, the conversion to chloride by Self's zinc dust method, gave low results in the time stated, 84.60 and 85.91%, being the values obtained on the special 1% solution, shown in Column 10. By modifying the conditions, as previously indicated, better results were obtained, 99.90-99.75-99.95%. These are shown in Column 11.

The Iodometric method has been discussed at some length and the results in Column 12 show that a little error creeps in, even if the alkali is added drop by drop, the method being otherwise exactly as described by Rupp. The good results, indicated in Column 13, were obtained by using an equivalent amount of alkali of *one-tenth* the strength of that recommended by Rupp, and adding slowly drop by drop.

Column 14 shows a value of 36.4% obtained by adding the reagents in the order indicated by Kolthoff, and values of 59.1 and 62.4% when the alkali was added last.

The comparative series of tests, using one common solution is interesting and serves to show which methods of those examined are the most reliable. It was a matter of interest to see that at least four or five of the methods listed in the adjoining table, which methods are all mentioned in the literature, were not reliable as they stood. Certain modifications gave good values for all except the method of splitting up the chloral by means of MgO, which method appears to be unreliable.

Those methods considered fairly satisfactory then, were those, the results of which are given in the table under Columns 1, 3, 9, 11, and 13. The average value of these five satisfactory results is found to be 99.54%, which may be taken as the degree of purity of the sample used.

The suggested modification of Archangelsky's method gives results a little low, but considering the necessary evaporation of large volumes of distillates, and the attendant loss of formic acid, and considering also the order of accuracy of the methods at present commonly in use, they may be considered quite fair.

TABLE OF COMPARATIVE VALUES

Titration with Alkali.		Treatment with Alkali and reduction of Mercuric Chloride.					Estimation as Chloride.				Iodometric methods.		
30 cc. N/10 at room temp.	sl. excess N/10 at 15° C.	NaOH diff. times and strengths.	NaOH modif'n of Arch's method.	NaOH boiled. Arch's method.	MgO refluxed.	MgO in cold.	Alcoholic KOH refluxed.	Alcoholic KOH closed bottle.	Zn dust. Self's method.	Zn dust and acid.	Rupp's method. N-soda added slowly.	Modified method. N/10 soda added slowly.	Kolt-hoff's method 2N-soda.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)
99.3	98.7	99.36	99.04	99.73*	92.88	96.84	96.23	99.54	84.60	99.90	98.25	99.49	36.4
99.3	98.7	99.44	98.72	107.0*	92.40	97.80	95.31	99.84	85.91	99.75	98.66	99.49	59.1
		99.40		150.5				99.77		99.95	99.41		62.4
		99.40		148.5				99.38					
				131.0									
Mean values.													
99.30	98.70	99.40	98.88	....	92.64	97.32	95.77	99.63	85.25	99.87	98.77	99.49	....

*Conditions of heating were different, and special solution not used for these tests.

Average of Columns	(1)	99.3
	(3)	99.4
	(9)	99.63
	(11)	99.87
	(13)	99.49
Mean.		99.54

Summary

(1) Archangelsky's method of determining chloral hydrate in organs and tissues, has been modified to give more reliable results. Values obtained by the old method ranged from 100% to 150% of the amount taken; by the new method uniform results about ½ to 1% low were obtained.

Twelve hours steam distillation appears to remove all but traces. It is advisable to distil, however, until no reducing action is observed on mercuric chloride.

(2) Kippenberger's method is reviewed and criticised. A theoretical objection is advanced.

(3) The determination of formic acid produced on refluxing with MgO is unreliable as a means of assay of chloral hydrate. Magnesium formate is unstable when boiled, and low results are always obtained.

(4) The low results attributed to the method of refluxing with alcoholic alkali and subsequent determination of chloride were confirmed. Good results were obtained, however, when the conversion was effected in a bottle under pressure.

(5) The conversion to chloride by zinc dust (Self's method) was found to be incomplete in twenty minutes, but good results were obtained when slightly modified.

(6) The volumetric method was applied under certain stated conditions, and a curve shows how long a contact with alkali may safely be made, to avoid secondary reactions.

Self's suggestion of applying a chlorine correction, gives good results if done in the cold, but is inexact at boiling temperature.

Garnier's method appears to give results just short of completion. A slightly higher temperature and a larger excess of alkali gave better results.

(7) The iodometric method of Rupp was found to give low results, even when the alkali was added last, according to his later instructions. By diluting the alkali to ten times the volume, and then adding drop by drop with constant shaking, a theoretical result was obtained, interfering secondary reactions being thereby reduced to a minimum.

Kolthoff's method was subject to the same criticism as that of Rupp.

(8) A comparison of the various methods, all of which appear in the literature, shows that several are inexact. Modifications have been suggested to the methods of Archangelsky, Rupp and Self, which appear to improve the results.

Acknowledgment

In conclusion I wish to express my indebtedness to Professor M. A. Parker for the suggestion of this investigation, and for helpful advice and criticism during the progress of the work.

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THE DATURAS

By Fred B. Kilmer, Ph. M.

"From Greenland's icy mountains
From India's coral strand,
Where Afric's sunny fountains
Roll down their golden sand,
From many an ancient river
From many a palmy plain

. . .

Till like a sea of glory,
It spreads from pole to pole."

THE DATURAS are woven in the myths, in the lore, in the legends, in the records of religion and of medicine of every land and of every people from prehistoric man to now.

The Asiatic "metel nut" is the species that figures most prominently in history. Linnæus gave as the habitat "Asia-Africa." He describes it as with "nodding globose pericarps."

Much confusion has arisen from the fact that botanists substituted for the name given by Linnæus the name "datura fastuosa," and transferred the Linnæus designation to the American plant, which is quite distinct from the datura metel.

Wherever found, the daturas first appear conspicuously in symbolism and in religious ceremonies. They were early recognized as intoxicants and as poisons.

The Arabian medical authorities state, in respect to Nux Methal, that "its taste is pleasant and unctuous, and its virtues cold in the fourth degree. If given in a small dose, it intoxicates strongly, and if two drachms are given, it proves fatal at once."

Rhazes describes the plant as "narcotic, sedative and perhaps an emetic medicine." He states that "it is a dangerous medicine which induces stupor, nausea, vomiting and inebriety."

Avicena says that "it inebriates, induces stupor, and is inimical to the brain and heart."

The Hindoo physicians held that the metel nut was "Alexiterial." "He who partakes of it is deprived of his reason, for a long time laughing or weeping or sleeping, with various effects, and oftentimes talking and replying; so that at times he appears to be in his right mind, but being really out of it and not knowing the person to whom he is speaking nor remembering what has happened after his alienation has passed. Many mundane ladies are such mistresses and adepts

in the use of this seed that they give it in doses corresponding to as many hours as they wish their poor victim to be unconscious or transported. And, truly, if I were to tell stories of what I have seen or heard relating to this matter and the different ways I have seen people act when under the influence of the drug, I would fill many sheets of paper, but as this is not necessary I will refrain. I will only say that I have never seen any one die from its effects, but I have seen some who have gone about for several days perturbed, and this must have been because it had been given to them in too large doses, which, if too great, will cause death, because this seed contains venomous parts."

In the Chinese, Japanese and Sanskrit literature the methal nut appears.

Entwined in the history of every race we find a story of the use of some variety of datura, ceremonially and medicinally. If a new continent were to be discovered, peopled with an unknown race, it seems probable that some kind of datura would be found, with a name and a legend as to its properties and uses.

The Far Eastern lore of the daturas goes back of the written records.

In the early Arabic literature we find jouz-mathel (metel nut), likewise datora tatorah. In Sanskrit, we have dhustura or umata. In East India, unmata, unmeta, dhatura, the German equivalent being Dotter.

According to Taoist tradition this name is derived from one of the Polar stars. Every messenger from the star carries in his hand a flower from the datura.

In Japanese literature the plant is known as "chosen-asagao" or the Korean morning-glory.

The early Greek writers refer to Nux Methal, which is believed to be the Eastern datura. They also use the designations—neura, neurada, neuada, neurata, nexuada, neurida, and poteriuni, which may have been intended for either the daturas or the mandragora.

In the Middle Ages the term "Hippomanes" was applied to the daturas.

The derivation of the word "stramonium" is not clear. The early writers applied it to several varieties of datura. It seems to have had a meaning somewhat the equivalent to the English term "raving night shade."

From the thorny fruit of the daturas arose the name thorn apple—German, dornappel; French, pomme epineuse; Dutch, doornappel. In

French there also appear the names pomme de diable, epineuse and herb aux sorciers.

The name Jimson Weed is a corruption of the name Jamestown weed, the designation of the American species noted by the early Colonists as growing near Jamestown, Virginia. From its peculiar odor the plant was given the name "stinkweed."

The name datura was given to the genus by Linnæus, in which he Latinized the East Indian name Dhatura, using in explanation a pun: "Daturæ, licet originis sit peregrinæ, vocabulum persistere valet, cum a latina derivari potest; dantur et daturæ forte in Indiis posthac semina a lascivic maritis inertibus." (*Linnæus,* Hort. Cliffort, p. 56, 1737.)

East Indian Datura

The datura metel, of the species believed to be identical with the nux methal and the hippomanes of the ancients, is very common in India, growing sometimes to a considerable size. Here are found the single white flower form (D. metel L.) and the double flower (D. metel fastuosa), the so-called black datura, with dark brown or black stems. There appears also here a variety with double red flowers and lead-colored foliage. The flowers of these species are sometimes expansive.

Peculiar to the nightshade instinct the flowers do not open during the heat of the sun; they open fully in cloudy weather, at nightfall, and remain expanded during the night. The odor of the flowers is not marked, but sweet, resembling the fragrance of the lily. All bear the peculiar green fruit or "nut" similar to small apples with spines. Upon ripening the fruit opens into four parts, exposing upon the white pith an abundance of wrinkled ear-shaped seeds.

In tradition and lore, in religious ceremony, in criminal narrative and in medicine, the seeds of the methal appear through the centuries.

The first travellers in the Indies note the universal presence of the plant, a knowledge of its narcotic properties and its use to increase the intoxicating powers of liquors.

The methal seeds through the ages have formed a potent criminal weapon. A nineteenth century author states: "The records of the courts of justice show that these seeds are still employed for the same licentious and wicked purposes as they were in the time of Acosta and Rumplinus." The seeds are used by thugs to stupefy their victims. They are used raw or roasted, mixed with flour, sugar and tobacco.

An essence is prepared "ten drops of which is sufficient to render a man insensible for two days."

The Hindoo physicians held that the name could be interpreted to mean "a remedy," "a destroyer of miasma," or it might relate to a poison.

Cristoval Acosta (1578) states that in the Orient it was employed as an aphrodisiac. "Among the Hindu enamorades few were without Datura seeds among their most highly prized treasures."

The daturas seem to have reached the Continent of Europe from the East. The Datura stramonium (our Jamestown weed) was in the sixteenth century cultivated in the gardens of Europe and England as an ornamental plant.

Mathiolus confused the term datura stramonium with datura metel, as did many other writers.

American Daturas

Hernandez, the sixteenth century medical explorer, who Rusby-like journeyed through New Spain, found in Mexico a plant called by the natives "Nacazcul," "toloazin," and "toloache," which has since been designated as the datura iunoxia Miller.

Hernandez found this and other daturas to be highly esteemed by the natives medicinally and ceremonially. From the seeds they made with pitch a plaster compound used in alleviating pains. From the leaves came a poultice to which they added capsicum as well as an anodyne infusion of the drug for external use. The user was cautioned that an excessive use would bring on "various and vain imaginations and madness."

We here have a primitive and independent equivalent of the modern plaster containing mydriatic drugs and capsicum.

The conquering armies of Cortez found the Aztecs of Mexico, a people whose civilization had developed from a primordial to a state of paralleling that of ancient Egypt.

In their religion and in their medicine, quite independently of European influence, they made use of the seeds of a plant identical with, or closely allied to datura metel.

An early writer says: "They have also great superstitions regarding a lentil-like seed which they call ololiuhqui, and also another larger drug, a root called peyote, which they venerate as though they were divine; for in drinking these herbs they consult them like oracles

regarding whatsoever maladies they may attempt to cure and whatsoever objects they wish to know about, whether lost or stolen, and those things which are beyond human knowledge, such as the origin of infirmities, especially if they are chronic and of long standing, and are attributed to witchcraft. In order to dispel doubts regarding this, and also for other purposes, they have recourse to these herbs through the medium of their imposter medicine men, who, after drinking, reply to all their questions. The person who practices this office is called "payni," which signifies the drinker of a syrup. They also pay these persons very well; and if the medicine man is not very skilful in his office, or if he wishes to excuse himself from the trouble which the drinking of these philters would cause, they advise the sick to drink them or those in quest of lost objects who seek to discover where those things are or in whose possession they may be."

Hernandes, by reason of its trumpet flower, placed it among the morning-glories, and on account of its deadly power purposely omitted recording its place of growth.

Jacinto de la Serna wrote of it: "These seeds they hold in great reverence as though they were God, burning candles before them and keeping them in small boxes, expressly made for this purpose; and they place sacrificial offerings to them on the altars of their oratories, or on the canopies over them, or in other secret places in their houses, so that when a search is made for them they cannot easily be discovered; or they may place them among the remains of their ancestors, which they leave to guard them, or, as it were, chained to them. And all this they do with such respect and reverence that when those who keep this seed in their possession are arrested or are asked for the paraphernalia with which they perform the ceremony of this drink, such as the little gourds and cups used to hold it, or for the seeds themselves, they protest most vehemently that they had no knowledge of the matter whatever, not so much from fear of the judges before whom they are arraigned as for the reverence they feel for the sacred objects, which they do not wish to affront by a public demonstration of the ceremonial use of them."

Amid the ruins of the ancient people who once filled the Southwestern United States there is found the seeds and seed pods of the daturas, and their use as an intoxicant and hypnotic still prevails among the Indian tribes of Utah and Southern California.

In gathering the plant for ceremonial or medicinal purposes, it is treated with great deference by the Luiseno Indians, who observe

preliminary ceremonies, recalling the customs of certain Mexican tribes in gathering the narcotic peyote, and those of European herb gatherers of the Middle Ages in connection with the dreaded mandragora. Before beginning to dig it up the medicine man addresses the plant somewhat as follows: "I have come to get you, but not without a purpose. You were placed as medicine, and it is for medicine that I seek you. Be not humiliated, oh, powerful one."

According to Dr. John P. Harrington, of the Bureau of American Ethnology, the uses of this plant in religious ceremonies and in medicine were quite distinct in the minds of the Indians. After having partaken of it ceremonially a man not infrequently would remain under its influence for two days, during which time he was left to himself. On regaining consciousness he was given warm water to drink and toward nightfall some gruel. Among the visions experienced by him while under the influence of the narcotic might perhaps be that of some particular animal or plant, which was not infrequently adopted as a supernatural helper or familiar spirit to accompany him through life and render him aid in times of doubt or trouble. For a month after having partaken of the drug it was customary for him not to go to bathe or to eat meat or fat and during this period the society of human beings was avoided and solitude was sought among the hills. The winter season was chosen for the administration of the drug; it was supposed to be injurious if taken in warm weather.

The initiation ceremony in which the plant is used is elaborate. When it grows dark the masters of the ceremony go from house to house to collect the candidates for initiation. The strictest silence is observed. A large stone bowl is placed before the chief, who, sitting in the darkness, pounds with a stone mano, or pestle, the dry scraped root of the plant to the accompaniment of a weird chant, while the boys stand waiting. The powdered root is then passed through a basket-sieve back into the stone bowl and water is poured upon it. The boys are enjoined to keep silence. As each boy kneels in turn before the big bowl to drink the infusion, his head is supported by the hand of the master of ceremonies, who raises it when enough has been taken.

It is a solemn occasion, a spiritual rebirth, suggesting the religious rites of baptism or confirmation. During the entire ceremony both the men and the boys are quite nude. When the drink has been administered to all the candidates, dances are performed in the darkness, accompanied by cries in imitation of birds and beasts, and when

these are finished the candidates are marched round a fire, chanting a ceremonial song.

As the effects of the narcotic plant overcome them, one by one they fall to the ground and are carried to another place and left until they regain consciousness. After this the dancing is resumed and kept up through the entire night. At daylight they return to the place where the drink was administered, and after a day of fasting they witness feats of magic performed by the shamans, from whom, after having been dressed in feathers and painted, they receive wonder-working sticks. The boys are also instructed by their elders in certain mysteries and rules of conduct, somewhat corresponding to one's duties toward God and to one's neighbor, as taught in the catechism. The initiatory ceremony is followed by two or three weeks of abstinence from salt and meat, after which a ceremony with a rope, called wanawut, is performed. When this is finished the candidates are free.

"The joyful news out of a new-found world," America, as recorded by the early explorers, was in part a description of certain narcotic solanums.

Here, independent of all knowledge of the Asiatic or European daturas, the savage tribes gained a knowledge of their peculiar properties and utilized them ceremoniously and medicinally, quite along the same lines as has been done elsewhere in the world.

The great variety and the abundant growth of the daturas on the American Continents, has led to the suggestion that this continent is the first home of these plants, and that prehistoric explorers carried the "sacred" seeds in their migrations to the Eastern Continent. Other suggestions are the reverse—that in some way the Eastern plants were transported to the West. Another guess might be that as it is probable the continents were at one time joined, from this they could easily be diffused over the earth.

The American daturas range over the continents, varying from shrubs to small trees. The species described under the name datura stramonium by early European botanists, undoubtedly in the main refers to other varieties than the Jamestown weed. The plant, however, was transported to Eastern lands in the very early days after the discovery of the Western continent. In the fifteenth and sixteenth centuries the Jamestown weed was a cultivated ornamental plant in the gardens of Europe. The Jamestown weed is undoubtedly an American creation, a solanum which found a favorable home in the

United States. With its allies, it without doubt forms a group distinct from other daturas. The "thorny apple of Peru" is believed to be very closely allied to, if not identical with, the Northern purple flower—datura stramonium tatula.

The Campindlas or Floripordroes of the South American Continent have been placed in a distinct genus, but many botanists class them as daturas. When compared with the brush or shrub forms of the daturas they are trees.

The natives of the South American Continent have long been aware of the narcotic properties of these plants. The priests of the Temple of the Sun at Sagamoza, now in the Republic of Colombia, were observed by Humboldt as preparing a narcotic drink called "touga," from a red flowered datura (D. Sanguinea).

In the Peruvian Andes tree daturas are found growing and fruiting at altitudes ranging up to 12,000 feet, where there was frost every night of the year.

The Mexican Torna-loco "maddening weed" is an aquatic datura.

In close alliance with the daturas are the climbing solandras found in the tropical Americas (also Australasia). These plants contain a mydriatic alkaloid—solandrine. The climbing solandras were cultivated in the ancient pleasure gardens of the Aztecs. The fragrance of the flower resembles that of the lily. The water contained in the unopened flower buds of these plants is used by the Indians in affections of the eyes.

Summary

The following, in part, follows a discussion of "Daturas of the Old World and New," by William E. Safford, in the report of the Smithsonian Institution, 1920, pp. 537, etc.:

The family Solanaceæ includes a number of narcotic plants, some of them of Old World origin, others belonging to the New World, which have been used from remote antiquity as intoxicants and medicines.

These plants owe their virtues to certain mydriatic alkaloids, principally to atropine, hyoscyamine and scopalamine, to which may be added the more recently discovered solandrine, or nor-hyoscyamine.

A feature in connection with these plants is the independent discovery in remote parts of the world of their remarkable narcotic effects, which have been attributed to magic, or to supernatural agencies, and have caused them to be regarded with dread.

Scarcely less remarkable is the independent utilization of distinct species in both the Old World and New in religious ceremonials, especially in oracular divination, in the discovery of hidden objects, and the foretelling of future events.

The use of endemic plants of America by the magicians and medicine men of various native tribes illustrates, in the most striking manner, the process of discovering the virtues and the utilization of plants of primitive people, and throws valuable light upon the early history of magic and medicine.

For a classification of the daturas and descriptions of new species reference may be made to Synopsis of the Genus Datura, in the *Journal of the Washington Academy of Sciences,* Vol. II, pages 173-189, 1921.

Our despised "Jimson Weed" assumed prominence during the World War, at which time the solanaceous drugs, especially belladonna, became very scarce. It was then found that this plant was a valuable source of atropine.

It is notable that the United States Pharmacopœia recognizes only one species of the Daturas—Datura Stramonium—thereby excluding other species of equal or greater value for medicinal use.

The Pharmacopœia likewise excludes all parts of the plant except the leaf—this in the face of the fact that it has been shown that the leaf contains the lesser proportion of the mydriatic alkaloids.

The story of drug plants is not yet complete. There is yet much to be learned, even as to the Daturas.

THE MERCURATION OF PHTHALEINS IN NEUTRAL SOLUTION WITH BICHLORIDE OF MERCURY

By Frederick R. Greenbaum, D. Sc., Chicago, Ill.

THE GREAT INTEREST aroused in the preparation of "Mercurochrome," a hydroxymercuridibromfluorescein, undoubtedly justified additional research on the introduction of mercury into phthaleins.

The introduction of mercury into phthaleins was patented by the Fahlberg List & Co.[1] and August Klages.[2] According to this patent the introduction of mercury into four halogenated phthaleins as tetraiodophenolphthalein, tetrabromfluorescein, tetraiodofluorescein, and dibromfluorescein was accomplished by means of mercuric chloride; particular emphasis was laid upon the fact that the action of mercuric chloride must take place in neutral solution. An excess alkalinity had to be avoided. In 1920 Edwin C. White,[3] of the Johns Hopkins Hospital, published his investigations on the introduction of mercury into phthaleins, which resulted in the synthesis of "Mercurochrome"; and since that time "Mercurochrome" has been investigated clinically and is today an important drug.

White stated, in his paper, that mercury will go into the ortho position to the hydroxyl, and that if the four ortho positions are occupied as in the case of eosine and others, mercury cannot be substituted by the methods which he employed. He used in his experiments mainly mercuric oxide and mercuric acetate as mercurating agents.

This investigation, however, shows that well-defined mercury compounds, either mono (most of the times monomercury compounds) or dimercury compounds, are obtained if the conditions described in the patent are closely adhered to in accordance with the claims of the patent.

The following are a list of the mercury compounds of phthaleins in which the four orthopositions were occupied, as well as in those in which one or two ortho positions were left vacant as: monochloromercuridinitrophenolphthalein, monochloromercuritetraiodophenolphthalein, monochloromercuritetrabromfluorescein, monochloromercurinitro metacresolphthalein, mono and dichlormercuridinitrofluorescein, dichlorodimercurigalleine and monochloromercuritetraiodofluorescein were prepared. Of these compounds only monochloromercuritetraiodophenolphthalein and the monochloromercuri-derivative of the tetraiodo and tetrabromfluorescein are described in the abovementioned patent.

The mercury in the compounds obtained was analysed according to White's method.[4]

Experimental Part

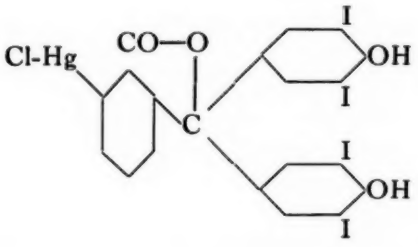
Monochloromercuritetraiodophenolphthalein.

The tetraiodophenolphthalein was prepared by the well-known method of Alex. Classen and W. Loeb,[5] and the pure compound was used for mercuration in the following way: 8.22 grams of tetraiodophenolphthalein and 1 gram of anhydrous sodium carbonate were ground together, and dissolved in 20 cc. of hot water. The solution was filtered and brought to a boil. Twenty grams of mercuric chloride was dissolved in 100 cc. of water, brought to a boil, and to this solution was gradually added the blue solution of tetraiodophenolphthalein. Immediately a yellowish-brown precipitate was formed. This mixture was kept boiling for one-half an hour, allowed to settle, decanted from the supernatant liquid, and washed three times by decantation with plenty of hot water to remove the great excess of mercuric chloride. The compound was then filtered, washed thoroughly with water until the washings did not contain any mercury, dried on a steam bath, and finally dried in a drying oven at 110° C. The compound was then analysed.

The iodine in the mercuriodophthalein was determined by the following method: 0.1 g. of the substance was decomposed by the Carius method. The decomposition required about 16 hours of heating in a closed glass tube in which the substance, silver nitrate, and concentrated nitric acid were placed. After decomposition the obtained precipitate consisted of silver iodide and silver chloride, as the compound also contained chlorine. The precipitate was filtered off, washed, dried and weighed. Then the precipitate was washed in cold, dilute ammonia which dissolved all the silver chloride and left most of the silver iodide. The method is not absolutely quantitative as the silver iodide was slightly soluble in the dilute ammonia which explains the discrepancy between the theoretical figure and the one obtained. However, the result of the analysis showed sufficiently that after mercuration no iodine was lost and that the four ortho positions were still occupied by the halogen. In spite of this, mercuration took place. Hence one may be justified in assuming that the mercury went into the phthalic acid ring.

The analysis gave 19.34% for mercury, and 44.66% for iodine. The theoretical for the mercury was 18.92%, and for the iodine 48.06%.

The analytical results led to the formula:

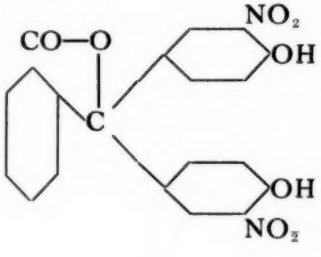


The monochloromercuritetraiodophenolphthalein was a yellowish-brown powder, insoluble in water and in all the other ordinary solvents. Soluble, however, in dilute alkalies with a blue color. It was stable towards ammonium sulfide in the cold, but on standing a small amount of mercury was thrown down.

The next mercuration product was *monochloromercuridinitrophenolphthalein.* The starting material for this mercury compound was dinitrophenolphthalein, and was prepared by dissolving or suspending 100 grams of phenolphthalein in 1000 cc. of glacial acetic acid, and then gradually treating, under cooling and stirring, with a mixture of 70 parts of nitric acid (sp. gr. 1.48) and 210 parts of concentrated sulphuric acid. Care was taken that the temperature remained at 20° Centigrade. The liquid after all the acid had been added got slightly warm, and upon cooling and standing a yellow crystalline nitro compound of phenolphthalein was precipitated. This compound was filtered, washed, recrystallized once from boiling glacial acetic acid and dried. It represented a dinitrophenolphthalein with a melting point of 196° C.

The analysis for nitrogen gave 6.75%, 6.93%; while the nitrogen calculated was 6.86%.

Therefore, the compound would probably have the following constitution:

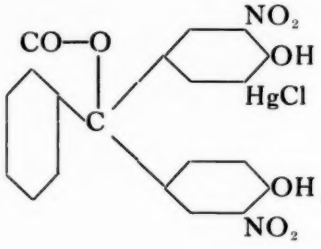


The dinitrophenolphthalein was a yellow crystalline substance, insoluble in cold or hot water, soluble in caustic soda solution with an orange color. It was slightly soluble in methyl and ethyl alcohol, slightly soluble in ether, and easily soluble in hot glacial acetic acid from which it could be recrystallized.

This dinitrophenolphthalein was then mercurated in the following way; 20.4 grams of dinitrophenolphthalein was ground with 5.4 grams of anhydrous sodium carbonate and dissolved in 200 cc. of water, boiled and filtered. Then 81 grams of mercuric chloride was dissolved in 250 cc. of water and heated to a boil. This boiling mercuric chloride solution was now slowly added to the neutral boiling solution of dinitrophenolphthalein. The resulting precipitate was kept boiling for one-half an hour, decanted, and washed by decantation three times with hot water, filtered, and washed thoroughly until the wash water was free from mercury. The precipitate was then dried on a steam bath, and finally dried at 110° C.

The analysis for $C_{20}H_{11}O_8N_2HgCl$ gave 4.49% for nitrogen and 30.80% for mercury. The calculated value for nitrogen was 4.36%, and for mercury 31.15%.

Hence the compound may be assigned the following formula:



A monomercury compound was formed in spite of the fact that two ortho positions were available. It represented a yellow amorphous powder, insoluble in the usual solvents, but soluble, however, in sodium hydroxide with an orange color to a perfectly clear solution which will not split off mercury. The alkaline solution will not precipitate mercury with ammonium sulfide.

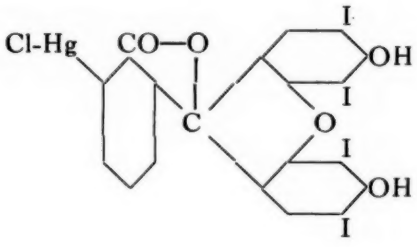
The next mercury compound was *monochloromercuritetraiodofluorescein* (monochloromercuryerythrosin). Ten grams of erythrosin (Eastman Kodak Company) (This compound was of the greatest

purity. The analysis for iodine by the Carius method was 59.95%. The theoretical value is 60.9%) was dissolved in 1 gram of sodium hydroxide and 100 cc. of water, filtered and heated to a boil, and to this hot solution was gradually added a boiling solution of 65 grams of mercuric chloride and 200 cc. of water. This mixture was boiled for half an hour, filtered, washed thoroughly with hot water, dried, and extracted with ethyl alcohol in a Soxhlet apparatus for eight hours to remove the excess unchanged dye. The extraction was continued until the alcohol appeared colorless. Then the compound was washed several times with hot water and dried at 105° C.

The analysis of this compound gave 18.73% for mercury and 44.2% for iodine. The theoretical percentages were 18.70% for mercury and 47.4% for iodine.

The method of analysis for the iodine was the same as in the case of tetraiodophenolphthalein, and the discrepancy of the figures obtained was due to the slight solubility of silver iodide in dilute ammonia, but even at that it shows distinctly that no iodine was split off during the mercuration, and as the four ortho positions remain occupied the mercury enters into the phthalic acid ring.

The structural formula for this compound may be as follows:



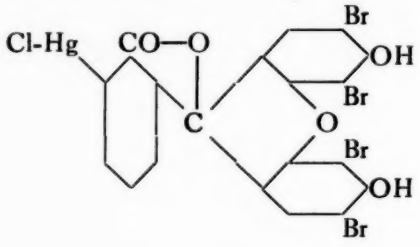
It represented a red amorphous powder, insoluble in cold and hot water, soluble in dilute sodium hydroxide or potassium hydroxide, insoluble in all common organic solvents.

Very much related to erythrosin is eosin, a tetrabromfluorescein, and was the next phthalein used for mercuration. *Monochloromercuritetrabromfluorescein* (monochloromercurieosin) was prepared from pure eosin. 12.8 grams of eosin was ground up with 2.4 grams of anhydrous sodium carbonate and dissolved in 100 cc. of water. This solution was boiled, filtered and gradually added

to a hot solution of 80 grams of mercuric chloride and 250 cc. of water. Then boiled for one-half an hour, decanted, filtered, washed with hot water until free from inorganic mercury, and extracted with ethyl alcohol and acetone for several hours in a Soxhlet apparatus until the solvents remain almost colorless. The compound was then dried and analysed.

The analysis of $C_{20}H_7O_4Br_4HgCl$ for mercury was 22.24%. The theoretical amount for mercury was 22.66%.

The formula for the compound formed may be as follows:



It was a red powder insoluble in water, ethyl alcohol and in all common organic solvents, but soluble in hot glacial acetic acid, and also in sodium or potassium hydroxide. The mercury of this compound will not split off in solution, and ammonium sulfide did not give a precipitate.

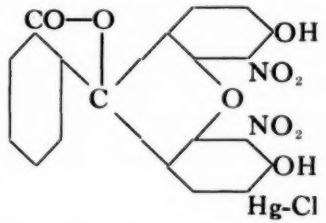
The next mercury compound was prepared from dinitrofluorescein. The dinitrofluorescein was obtained according to Beilstein [6] by nitrating fluorescein with fuming nitric acid. The obtained dinitrofluorescein was analysed for nitrogen and gave 6.90% and 6.51%. The calculated amount was 6.60%.

It was a yellowish-orange powder soluble in sodium hydroxide with a reddish-blue color, soluble in excess sodium hydroxide with a blue color, soluble in ethyl and methyl alcohol, slightly soluble in ether, and insoluble in cold or hot water.

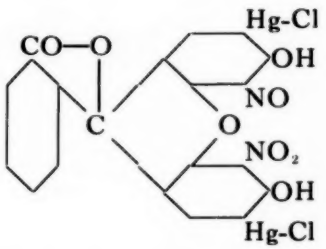
Mercuration was again carried out with mercuric chloride in the following way: 21.1 grams of dinitrofluorescein was dissolved in 4 grams of sodium hydroxide and 100 cc. of water, heated to a boil, filtered, and to this was added a boiling solution of 81 grams of mercuric chloride in 250 cc. of water. Precipitation occurred immediately and the mixture was kept boiling for one hour, then cooled and washed three times by decantation, filtered, washed with water until free from mercury, and dried on a steam bath. The compound

was finally extracted with ethyl alcohol and acetone in a Soxhlet apparatus, extracted with hot water, dried, and analysed. For a monomercury compound it should give 4.3% for nitrogen, and 30.7% for mercury. After the first extraction with alcohol, acetone, and hot water the nitrogen was found to be 3.14%, and the mercury 35.5%. Therefore the extraction was continued and the analyses between each extraction for four hours showed for nitrogen: 3.31%, 3.38%, 3.39%, and 3.38%. The corresponding mercury figures after the various extractions were: 33.9%, 35.6%, 36.4% and 36.4%. The nitrogen for a dimercury compound when calculated should be 3.1%, and the mercury 44.9%. These figures clearly indicated that the formed compound represented a mixture of mono and dimercury compounds of the following combinations:

I



II



This mixture represented an amorphous red powder insoluble in cold and hot water, soluble in ethyl alcohol, and soluble in sodium hydroxide with a brownish-blue tint though turning after a short time into a deep blue color. The mercury was firmly bound in the compounds as it did not split off after standing for several months. This phthalein was the only one that gave a mixture of a mono and a dimercury compound.

The next phthalein gave a monomercury compound, namely *monochloromercurinitro meta cresolphthalein*. Meta cresolphthalein was not described by Beilstein [7] and was, therefore, prepared in the same way as orthocresolphthalein: 270 grams of phthalic acid anhydride and 180 grams of metacresol were mixed, and to it was added 180 grams of stannic chloride. This mixture was then heated in an oil-bath at 125 to 130° C. for 8 to 10 hours. The fusion after cooling was steam distilled to remove the excess meta cresol, washed with hot

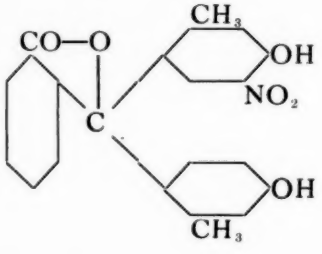
water to remove the stannic chloride, the residue was dissolved in 20% sodium hydroxide solution, and the resulting purple solution filtered. This solution was acidified with hydrochloric acid (1 : 1) and the light brown precipitate filtered, redissolved in alkalies, and re-precipitated with hydrochloric acid, filtered and washed free from HCl. The compound was then dissolved in methyl alcohol and boiled with charcoal for two hours. The charcoal was removed by filtration, and the yellowish-brown filtrate poured into a large amount of water, which on standing precipitated as a yellow powder the pure meta-cresolphthalein.

The compound was a yellow amorphous powder soluble in sodium hydroxide with a purple color, and was precipitated with mineral acids. It was soluble in ethyl and methyl alcohol, ether, acetic ether, and in concentrated sulphuric acid in which it dissolved with a light brown color.

This metacresolphthalein was nitrated in the same manner as phenolphthalein, but only a mononitrometacresophthalein was obtained.

The analysis for the mononitrcoresolphthalein gave for nitrogen 3.56%. The theoretical for nitrogen was 3.50%.

The mononitrocresolphthalein formed must have the following formula:

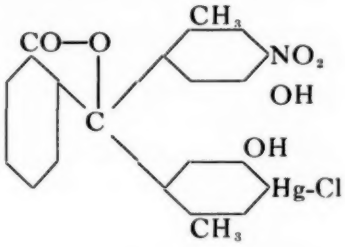


The compound was a brown amorphous powder, insoluble in hot and cold water, soluble in alcohol and ether, and soluble with a brown color in sodium or potassium hydroxide.

The mononitrometacresolphthalein was now mercurated in the same way as the first phthalein and yielded a *monochloromercurimono-nitrometacresolphthalein.*

Analysis of the compound for nitrogen gave 1.8% and 1.9%, and for mercury 32.1% and 31.8%. The theoretical amounts were 2.2% for nitrogen, and 31.2% for mercury.

Evidently a monochloromercurimononitrometacresolphthalein was formed and was assigned the following formula:

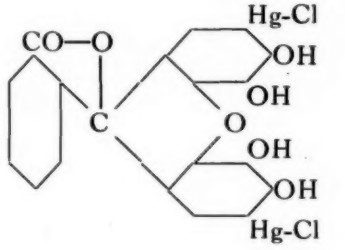


The compound was a dark brown amorphous powder insoluble in cold or hot water, alcohol, ether and all common organic solvents. It was soluble, however, in sodium hydroxide with a brown color, and did not split off any mercury on standing.

The next and last phthalein investigated gave a dimercury compound upon mercuration. Commercially available gallein, c. p. (of the Zinsser & Co.) gave on mercuration a *dichlorodimercurigallein.*

The analysis of the compound gave 48.40% for mercury while the theoretical was 48.13%.

Dichlorodimercurigalleine would have the following formula:



It represented a dark brown, almost black amorphous powder, insoluble in cold or hot water, alcohol, and all common organic solvents. It was soluble in glacial acetic acid and in sodium hydroxide with a dark brown color. No mercury split off on standing.

Summary

1. In this investigation the mercuration of phthaleins with mercuric chloride according to the German patent, D. R. P. 308335 of the Saccharin Fabrik Aktien Gesellschaft vormals Fahlberg, List & Co.

and the U. S. P. 1,455.495 August Klages was carried out and resulted in the formation of monomercury and dimercury compounds.

2. This mercuration will take place even when all four ortho-positions of the phenolic rings in the phthalein are occupied, the mercury in this case enters the phthalic acid ring. The reaction will only take place if perfectly neutral solutions of phthaleins are allowed to act with highly concentrated solution of boiling mercuric chloride.

3. Contrary to the findings of other investigators it was found that such phthaleins as tetraiodophenolphthalein, tetraiodofluorescein, tetrabromfluorescein (eosin) form well-defined monomercury compounds in spite of the fact that the four ortho positions were occupied. These compounds were described in the above-mentioned patents and in order to confirm their existence which was disputed sometime ago; these compounds were prepared and are described in this investigation.

4. Besides the mercury compounds mentioned under (3) the following new mercury compounds were prepared: Monochloromercuridinitrophenolphthalein, monochloromercurimononitrometacresolphthalein, dichloromercurigallein, and a mixture of mono and dichloromercuridinitrofluorescein.

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(2) U. S. P. 1,455.495, Feb., 1915.
(3) *J. A. C. S.*, Vol. 42, p. 2355, 1920.
(4) *J. A. C. S.*, Vol. 42, p. 2359, 1920.
(5) *Berichte der Deutseh Chemischen Gesellschaft*, Vol. 2, p. 1610, 1895.
(6) Beilstein, Vol. II, p. 2060, 1895.
(7) Beilstein, Vol. II, p. 1897, 1895.

PHYTOCHEMICAL NOTES

From the Laboratory of Edward Kremers.

No. 105. A PRELIMINARY STUDY OF DIGITALIS SEED

By S. H. Culter*

WHILE ENGAGED in the investigation of the sterol obtained from Echinacea, an attempt was made to prepare digitonin from digitalis seeds for further examination of the unsaponifiable portion of the fatty oil.

It was thought advisable to make a preliminary investigation on a small sample. Accordingly, two samples of 100 g. each were subjected to extraction by selective solvents with the following results:

Solvent	*Percentage of Extractive*
Petroleum Ether	31.5
	31.3 av. 31.4
Ether	0.93
	0.70 av. 0.81
Chloroform	2.7
	2.5 av. 2.6
Alcohol	11.7
	11.0 av. 11.35
	Total 46.16

The petroleum ether extract consisted of an amber-colored oil, while the other extracts were of a resinous nature.

A kilogram of ground digitalis seeds was extracted successively with the above solvents and then extracted with 50 per cent. alcohol in which digitonin is soluble. As already pointed out, the petroleum ether extract consisted of a fatty oil. This oil has been investigated by I. S. Mellanoff [1] who found the amounts of "Soluble fat acids," "Insoluble fat acids," "Liquid fat acids," etc., but did not attempt to isolate and identify any of the individual fatty acids. Hence it seemed desirable to make such an investigation.

304 g. of the oil were saponified with an excess of potassium hydroxide and the resulting soap solution extracted with ether.

*Lloyd Fellow.

[1] *Am. Jour. Pharm.* 99 (1927), p. 549.

5.7 g. of unsaponifiable material, which gave positive sterol color tests, were obtained. However, after several recrystallizations from alcohol, a sharp melting point could not be obtained. The product melted between 93 and 105° C. and must therefore be a mixture.

The saponified oil was acidified with sulphuric acid and again extracted with ether to remove the fatty acids which amounted to 246 g. The unsaturated fatty acids were separated from the saturated fatty acid by the difference of solubility of their lead salts.

The unsaturated fatty acids weighed 126 g. and required 35 cc. of bromine for complete saturation. The hexabromide fraction weighed 28.3 g. and had a melting point of 106°. After recrystallization from acetone the melting point remained constant at 113°. The bromine determination gave 54.34 p. c. and 55.15 p. c. respectively, or an average of 54.74 p. c. bromine as compared with 53.3 p. c. of bromine calculated for tetrabromide and 63.3 p. c. for hexabromide. Judging by the melting point and the bromine content, this fraction may be regarded as tetrabromide, indicating the presence of linolic acid. The tetrabromide fraction weighed 20.8 g. and gave a melting point of 110°. After recrystallization a constant melting point of 112° was found. The bromine determination gave 53.01 p. c. and 53.79 p. c. or an average of 53.4 p. c. of bromine which compares favorably with the calculated percentage of bromine as above stated. The dibromide fraction was debrominated by refluxing with powdered zinc in the presence of alcohol. The resulting product amounted to 100 g. It failed to give a positive color test for oleic acid and, when made alkaline with potassium hydroxide solution previous to oxidation with $KMnO_4$, the potassium soap was found to be insoluble in water. This would indicate the absence of oleic acid the potassium salt of which is soluble in water. Thinking perhaps some had gone into solution, the latter was treated with a 1½ p. c. potassium permanganate solution in an attempt to prepare the dihydroxy stearic acid, but negative results were obtained. There is, therefore, no evidence for the presence of oleic acid in the oil. Time did not permit of a further investigation of the water insoluble potassium soap.

The solid fatty acid fraction weighed 18.5 g. and, after recrystallization from dilute alcohol, gave a constant melting point of 52°.

The glycerol from the oil amounted to 28.2 g. It gave the odor of acrolein upon heating with potassium acid sulphate and prevented precipitation of cuprous hydroxide from a solution of copper sulphate

and sodium hydroxide. Both of these qualitative tests indicate the presence of glycerol.

The hydroalcoholic extract of the seeds, amounting to 7 g., was treated according to the procedure for the preparation of Homolle's digitalin (Schmidt, *Pharm. Chem.*, Vol. 2, p. 1878). The crystalline product obtained was only partly organic.

Time did not admit of a further study of the materials prepared.—(*Laboratory for Pharmaceutical Chemistry,* University of Wisconsin.)

MEDICAL AND PHARMACEUTICAL NOTES

POISONOUS PRINCIPLE OF PYRETHRUM—The poisonous principle of old-fashioned insect powder has been traced to its lair by C. B. Gnadinger and C. S. Corl, research chemists of Minneapolis. The powerful poison of the material has been located largely in the achenes, or fuzzy seeds, of the pyrethrum plant, from which it is prepared.

Pyrethrum, in reality a variety of chrysanthemum, has been used to abate insect nuisances for generations. The flowers, and even leaflets and stems of the particular species, are commonly ground into a fine powder which is extremely toxic to insects but harmless to man.

Sometime ago the noted Swiss chemist Staudinger solved the mystery of the chemical formula of "pyrethrin," the potent oil which gives the value to the insect powder. The oil is actually a mixture of two similar but complicated substances containing only carbon, hydrogen and oxygen, innocent elements when in simple relations. Being an oil, it may be diluted in gasoline or like solvent and used in sprays where dusting powders are undesirable.

The Minneapolis chemists have now discovered a method of chemical analysis whereby one may quickly tell which plants, and which parts of the plants, contain the poisonous principle. Armed with the new method, they have upset several long-standing beliefs in the insect-powder business. Japanese pyrethrum has been found to be just twice as potent as the classic and more expensive Dalmatian powder. Also the mature flowers are more valuable than the unopened or half-opened buds, which the trade prizes and holds at higher prices. Stems and florets have relatively little value compared to the achenes.

The extreme toxicity of pyrethrin was shown in the Minnesota experiments by test on cockroaches. A solution of one part of the oil in 80,000 of water effected a complete slaughter of a colony of the pests submitted to the test.

The perfecting of these chemical experiments opens the door to a most promising research in plant breeding. Just as the sugar content of beets was raised in cultivation, so may it be possible to increase the pyrethrin content of chrysanthemums. At present only about one-half to three-quarters of one per cent. of the powder is actual poison. Modern selection methods as practiced by plant breeders would probably lead to a great increase in efficiency in agricultural pest control. It is also considered possible that the essential principle itself may be made synthetically if the demand should be sufficient.

TALBOT'S SOLUTION OF IODINE—In consequence of the number of inquiries for a formula for Talbot's solution which have been received in connection with the iodine research work now being conducted at the college, the formula for this solution is given herewith:

Talbot's solution of iodine is a preparation frequently prescribed by dentists for the treatment of the gums and teeth in certain serious diseases of the mouth. The formula is as follows:

Iodine	5 drachms
Zinc Iodide	3 drachms
Water	2 fluid drachms
Glycerin	10 fluid drachms

Incorporate the iodine and zinc iodide, previously triturated together in the water and glycerine.

INJECTION OF IRON AND ARSENIC—During recent years the use of iron and arsenic as an intramuscular injection for anæmic conditions has grown in favor. The author, Chas. M. Caines, suggests the following formula of which 1 cc. contains approximately $\frac{1}{15}$ grain of iron and $\frac{1}{50}$ grain of arsenious anhydride.

Liq. ferri perchloridi fort. B.P.	1.75 cc.
Citric acid	2 gm.
Arsenious anhydride	0.13 gm.
Solution of ammonia	q.s.

Distilled water, sufficient to produce 100 cc.

—(*Br. & Col. Pharm.*)

CAPSICUM TINCTURE OF THE B. P.—Experimental work leads the authors, Messrs. Beardsley and Bolton, to the following conclusions: (1) The extent to which fatty matter is deposited at low temperatures from Tincture Capsici B. P. has been found to vary with the sample of capsicum used, and to depend on the fineness of the powder and the temperature at which it is macerated. (2) It is suggested that the most convenient way of preparing a tincture which will remain clear at low temperatures is to macerate the drug with 60 per cent. alcohol, and then to add sufficient rectified spirit to bring the strength of the tincture up to 70 per cent. alcohol.

A sample made using only bruised capsicum fruit, so that the seeds were practically unbroken, and 60 per cent. alcohol, did not

deposit at all on cooling to 0 degrees C. It had a total solids of 1.03 per cent. considerably less than that of the tincture made from finer powder, but its color and pungency were practically identical. This would be expected to occur if, as is stated in the B. P. C., the pungent principle was contained chiefly in the epidermal cells of the fruit, and the dissepiment which divides it into two parts: the seeds, too, are quite colorless. One way, then, of making a tincture which is stable at low temperatures seems to be to use only the bruised fruit.—(*Br. & Col. Pharm.*)

Cholesterol Hair-Lotions Against Loss of Hair—Experimenting on the living organism, Professor Jaffe, Frankfort-on-Main, has proved that there is a connection between the assimilation of cholesterol and the growth of the hair. In cases where the loss of hair is due to disturbed function of the sebaceous glands, the application of cholesterol in the shape of a hair-lotion is indicated and promising. The formation of scurf usually disappears after about two weeks, but obstinate cases often require prolonged treatment. During the administration of cholesterol the hair should not be washed too frequently in order to avoid irritation of the sebaceous glands. The solution of the cholesterol for hair-lotions often presents difficulties. Ether, chloroform, fats, and essential oils, all good solvents for cholesterol, are out of the question for this special purpose. Ninety-four to 95 per cent. alcohol dissolves at ordinary temperature 2 per cent.; 90 to 92 per cent. alcohol 1 per cent.; 85 to 87 per cent. alcohol 0.5 per cent. cholesterol. Seventy-two to 75 per cent. isopropylalcohol takes up 1 per cent.; 64 to 65 per cent. isopropylalcohol 0.5 per cent. A small addition of carbon tetrachlorohide increases the solubility of cholesterol and prevents it from separating out at changes of temperature. Formulæ: (1) Alcohol, 95 per cent., 89 gms.; glucerin, 3 gms.; cholesterol, 0.5 gm.; aqua dest., 6.5 gms.; perfume or essential oils, 1 gm. (2) Isopropylalcohol (for medicinal purposes), 66 gms.; glycerin, 3 gms.; cholesterol, 0.5 gm.; aqua dest., 29.5 gms.; perfume, 1 gm. (3) Alcohol, 90 per cent., 75 gms.; isopropylalcohol, 5 gms.; glycerin, 3 gms.; carbon tetrachloride, 3 gms.; cholesterol, 0.25 gm.; pure lecithin, from yolk of egg, 0.1 gm.; perfume, 1 gm.; aqua dest., 13 gms. Generally 0.2 to 0.3 per cent. of cholesterol will be sufficient.—(*Dtsch. Parf.-Ztg., 16,* 1930, 75, through *Duedd. Ap.-Ztg., 70,* 57, 402, through *Pharm. Journ.*)

NEWS ITEMS AND PERSONAL NOTES

RUTH E. MILLER CONTINUES IODINE RESEARCH—Ruth E. Miller, who received from the Philadelphia College of Pharmacy and Science a degree of Master of Science in Bacteriology in June, 1930, has been named to continue the research under the auspices of the Chilean Government in the pharmacy of iodine.

During the past year, Linwood Tice, Philadelphia College graduate of pharmacy in 1929, has held this fellowship, assisted in the bacteriological phases of the research by Miss Miller. Tice has just been appointed to the chair of Professor of Theoretical and Operative Pharmacy in Baylor University, Dallas, Tex.

The research this year will be conducted under Miss Miller's direction almost entirely in the field of bacteriology.

NEW FELLOWSHIP OFFERED AT PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE—For the college year 1930-31 the Philadelphia College offers a new graduate fellowship in pharmaceutical research. This fellowship is made possible by the co-operation of Eli Lilly & Company, pharmaceutical manufacturers, of Indianapolis. The fellowship carries with it a compensation of $750 and free tuition.

The candidate will devote himself to a study of enteric coatings for tablets and capsules.

During the past year, Milton Wruble, chemical engineering graduate from the University of Michigan, received his Master of Science degree from the Philadelphia College for original research in the field of enteric coatings for tablets. The purpose of the fellowship is to develop further the fundamental findings of Milton Wruble.

Candidates for the fellowship must hold at least the degree of Bachelor of Science in pharmacy, chemistry or related subjects to be eligible for consideration. Opportunity is afforded the holder of the fellowship to enroll for graduate courses leading to the degrees of Master of Science and Doctor of Pharmacy.

COUNTERFEIT ALLONAL—A counterfeit Allonal is being offered to the drug trade. The tablet bears a very close resemblance to the original in shape, size and color. Chemically it is different from Allonal and it cannot exert the same therapeutic action as Allonal.

The bottles, caps and labels are also counterfeit and are hardly distinguishable from the original.

We warn all members of the drug trade to purchase Allonal only from very reliable sources of supply.

In order to help us put an end to such nefarious practices which strike at the very health and life of the public, we offer one thousand dollars ($1000) reward for information resulting in the arrest and conviction of the counterfeiters.

If offered suspicious supplies, write, telegraph or telephone E. H. Bobst, care of Hoffmann-La Roche, Inc., Nutley, N. J.

THE 92 ELEMENTS—P. C. Kullman, 110-116 Nassau Street, New York City, have recently compiled a copyrighted folder, "The 92 Elements," giving their numbers, names, symbols, atomic weights, melting points, and years of discovery, as far as known. Copies of the folder can be had gratis upon request and upon mentioning the AMERICAN JOURNAL OF PHARMACY.

BOOK REVIEWS

ORGANIC AND FOOD CHEMISTRY. By Garry Eugene Culver, LL.D., and Thomas Arthur Rogers, B. S., Central State Teachers' College, Stevens Point, Wisconsin. 208 pp. P. Blakiston's Son & Company, Inc., Philadelphia. $1.50 net.

"This book, as it now appears, is the result of the experience of both authors in teaching the subject from typed notes through quite a long period of time." It is "mainly a compilation of matter selected from other texts, a list of which will be found at the end of this book." It is "designed primarily for teachers of domestic science," but others should find it useful.

The authors shoulder the responsibility for any errors, absolving from all blame the authors of the thirty-three texts from which selections have been made. Their editorial "shoulders" need not be particularly broad to carry the burden of errors so far as weight is concerned, but they may have considerable of a bill for "plate corrections" when they revise the book, because of the number of minor errors. It would be interesting to know where they got some of the chemistry they present, for it is not found in any of the many books with which the present reviewer is acquainted.

The book is essentially a laboratory manual, containing 133 so-called "Experiments," each of which requires the carrying out of three to a dozen or more "Tests." At the end of each of the nineteen chapters is to be found an exhaustive (perhaps some students would say "exhausting") list of "Questions for Review and Study," the "looking up" of which cannot fail to be helpful to the student who uses the book as a text. This means a lot of supplemental reading on his part; for furnishing the outline for such reading the book is worth all it costs for that feature alone. It would appear to have quite a large field of usefulness.

F. P. STROUP.

INORGANIC PHARMACEUTICAL CHEMISTRY. By Charles H. Rogers, D. Sc., Professor of Pharmaceutical Chemistry in the College of Pharmacy, University of Minnesota. 8vo, 676 pp., with 50 engravings. Lea & Febiger, Philadelphia. Cloth, $7.00 net.

In this work (intended "for students of pharmacy and pharmacists") the author has presented the elements and their compounds in

such manner as to make them especially interesting to the class of readers already mentioned. He gives the physical constants of inorganic compounds of pharmaceutical importance, considers collectively the chemistry of the elements and their compounds, and the pharmacologic actions of various ions and of pharmaceutical preparations.

Under a description of each chemical is a list of all the U. S. P. and N. F. preparations into which it enters, with a brief description of each preparation with a statement as to its function.

The book is not intended to replace a text on general chemistry, but would seem to serve best as a companion to the U. S. P. and N. F., explaining the reactions involved in the chemical processes of these two books, besides giving a lot of other valuable information. Laboratory methods for the manufacture and testing, qualitative and quantitative, are given for most of the compounds considered in the book.

As is generally the case with new books, a number of errors have escaped the proofreader, the majority of them being nothing more serious than the incorrect spelling of a word. A few of the more serious may be mentioned. "Baking Soda" is given as a synonym for Potassium Bicarbonate and not mentioned as a synonym for Sodium Bicarbonate. The formula for the official Ammonium Valerate is given as based on Normal Valeric Acid. In one place the composition of Aluminum Bronze is given as: "Copper, 90-98%, Aluminum, 2-10%," while on another page it is given as "90 to 98 per cent. Aluminum and 2 to 10 of Magnesium."

It has brought together a lot of information that, so far as this reviewer knows, cannot be found in any other one work; and thus the book should be a very useful addition to any pharmacist's "five-foot shelf."

F. P. STROUP.

A TEXT BOOK OF PHARMACOGNOSY. By Dr. Heber W. Youngken, Professor of Pharmacognosy and Materia Medica in the Massachusetts College of Pharmacy. 3d revised and enlarged edition. 817 pp., 367 illustrations. P. Blakiston & Son, Philadelphia. $6.00.

In the first chapter of part I we find a very brief (fifteen pages) discussion of fundamental considerations: general definitions, occurrence, handling, variation and evaluation of drugs, and historical facts including some recent biographical data.

The second chapter (thirty pages) gives, partly in tabulated form, the morphological classification of drugs and the specific definitions, titles, origins and general directions for the examination of drugs.

The taxonomic consideration of vegetable drugs, discussed in the first chapter of part 2, represents the main portion (almost 700 pages) of the textbook. Here the general groups furnishing drug plants are briefly discussed, followed by the detailed descriptions of the drug plants and drugs, in the main official in the Pharmacopœia and National Formulary. A general scheme is followed in the detailed discussion and enumeration of data, as: domestic and foreign synonyms, origin, part used, standard of purity, description of plants, production and commerce, descriptions of characteristic macroscopic and microscopic characteristics, of chemical constituents, medicinal uses, the average dose, the adulterants and substitutes. The descriptions of animal drugs are similarly treated in chapter 2. This is followed by an enlarged chapter (twelve pages) on microanalytical methods, including those for quantitative microscopical counts, measurements, micro crystals, microchemical tests and microphotography.

The author enjoys the distinction of a high standing in the professional field. The textbook is an evidence of his painstaking work to keep the data up to date. While he stresses the taxonomic side of pharmacognosy, he does not, as indicated in the brief outline above, limit the information to those facts.

ARNO VIEHOEVER.

ALLEN'S COMMERCIAL ORGANIC ANALYSIS, Vol. VIII, fifth edition. Edited by C. Ainsworth Mitchell, A. M., D. Sc., F. I. C., assisted by collaborators. 8vo, 733 pp. P. Blakiston's Sons & Co., Inc., Philadelphia, 1930. $7.50.

This volume covers a large amount of that part of chemistry now well known and much cultivated under the title "biochemistry." It concerns especially the medical chemist and toxicologist. The amount of important material requiring attention is so great that an additional volume will be required. This is in preparation and will doubtless be available before many months. C. O. A. took a dominant position in the field of analysis at its first appearance a half century ago and still maintains it. The preparation of the text has passed out of the ability of any one person and the present volume is the work of the eminent editor and equally eminent collaborators, four of whom are well-

known American specialists. Of the book as a whole it is simply necessary to say that like all its fellow volumes it is indispensable to the library of the practising analyst, works-chemist and clinical chemist.

The enormous development of industrial chemistry of recent years and the extensive invasion of chemistry into the ways of both peace and war have greatly multiplied the numbers of workers in these fields and caused even the descriptive and analytic literature to be largely infiltrated with technical matter, so that the present volume presents a much larger share of technology than the earlier editions. The great development of synthetic processes has brought new problems into the laboratory. This has been interestingly shown in connection with the synthetic production of secondary propanol (usually erroneously called "isopropanol") from natural gas. The current U. S. Pharmacopœia gives a test for the alcohol, but shortly after publication it was found that some samples will not react, and later the reaction was found to be due to tertiary butanol, which is not uniformly present. Obviously, the presentation of the tests for this propanol will necessitate some discussion of the technology, but care should be taken to restrict such data to the lowest possible extent. It seems to the reviewer that the section on the cyanogen compounds is unduly comprehensive, much technology and general descriptive matter being included. On page 479 it is stated that "hydrocyanic acid occurs in nature in combination as cyanogenetic glucoside." This is an inaccurate form of expression. Hydrogen cyanide is not preexistent in amygdalin any more than dextrose and benzaldehyde that are developed coincidently when the glucoside is hydrolyzed. In connection with the detection of hydrogen cyanide by the use of alkali-sulphides (as a matter of fact, ammonium sulphide is the best reagent) no mention is made of the simple arrangement by which the vapor of the compound can be used instead of adding the reagent to the mixture under examination.

The volume will be absorbed rapidly into the libraries of the many workers in the field to which it is devoted and will be a welcome aid to them. It is understood that another volume will complete the work, and then the editor's attention will be turned to the labor of preparing a new edition of volume I and so on.

HENRY LEFFMANN.